isohexane/EtOAc (1:0 to 4:1 gradient over 30 min) to give the title compound as a solid (150 mg, 100%). MS (ES+) *m/z*: 328 $(M+Na)^+$.

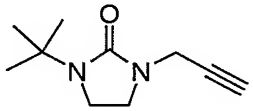
Preparation 251

2-Chloro-pyridazine

Add 3(2*H*)-pyridazinone (2 g, 22 mmol) to neat phosphorus oxycloride (4 mL) in a sealed tube and heat the mixture at 80 °C with stirring for 2 h. Add caustiously water (10 mL), saturated aqueous $NaHCO_3$ (50 mL) and solid Na_2CO_3 until pH= 9. Extract the mixture with dichloromethane (4 x 50 mL). Dry the organic layer over Na_2SO_4, filtrate and concentrate *in vacuo* to give the title compound as brown oil (2 g, 84%).

Preparation 252

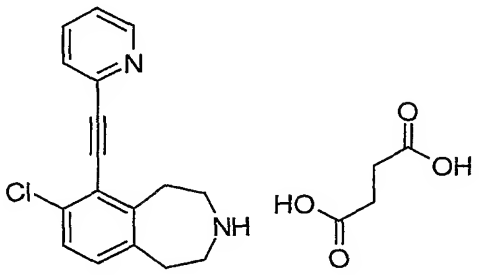
1-*tert*-Butyl-3-prop-2-ynyl-imidazolidin-2-one



Dissolve 1-*tert*-butyl-imidazolidin-2-one (2 g, 14 mmol) in anhydrous THF (60 mL) and cool at –78 °C. Slowly add *n*-butyllithium (6.8 mL, 17 mmol, 2.5 M solution in hexanes). Stir the solution for 30 min. Rapidly add propargyl bromide (3.2 mL, 28.2 mmol, 80% solution in toluene). Warm the solution to room temperature while stirring overnight. Concentrate the reaction mixture *in vacuo* and filter the residue on a short pad of silica gel eluting with dichloromethane/diethyl ether (1:1) to give the title compound as a yellow oil that solidifies on standing (1.77 g, 70%). GC-MS *m/z* (%) 180 (M^+, 7), 165 (100), 123 (12), 84 (17).

Example 528

7-Chloro-6-pyridin-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

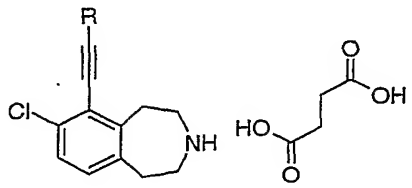


Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with 2-ethynyl-pyridine (0.20 mL, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40 min) to give 7-chloro-6-pyridin-2-ylethynyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (342 mg, 90%). MS (ES+) *m/z*: 379 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-pyridin-2-ylethynyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (60 mg, 0.159 mmol). Purify by SCX chromatography to give the free base of the title compound (33 mg, 73%). MS (ES+) *m/z*: 283 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound as a light brown solid (45 mg, 95%). MS (ES+) *m/z*: 283 $(M+H)^+$.

Examples 529-531

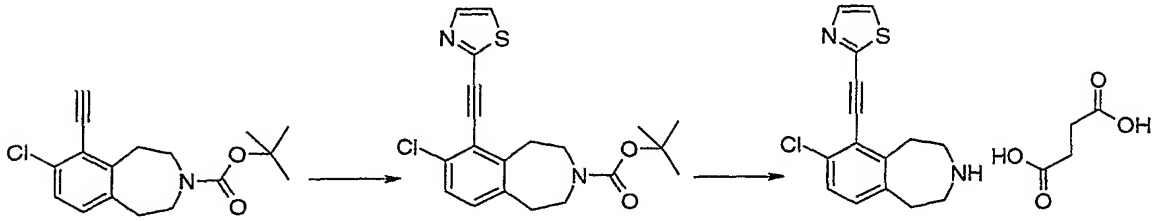
Examples 529-531 may be prepared essentially as described in Example 528 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alkyne. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*	
529	3-Pyridyl	7-Chloro-6-pyridin-3-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	78	283 $(M+H)^+$	
530	4-Pyridyl	7-Chloro-6-pyridin-4-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	84	283 $(M+H)^+$	
531	2-Thiophenyl	7-Chloro-6-thiophen-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	95	288 $(M+H)^+$	

Example 532

7-Chloro-6-thiazol-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

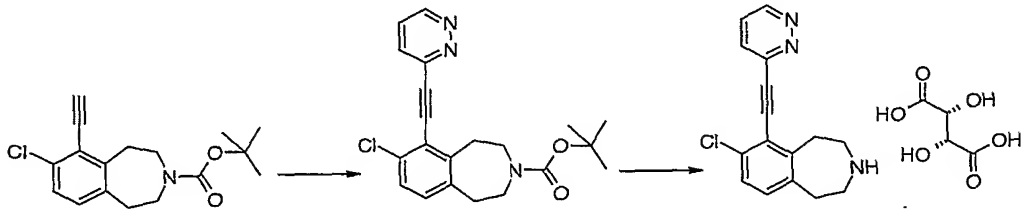


3-*tert*-Butoxycarbonyl-7-chloro-6-(thiazol-2-ylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 8 to couple 2-bromo-thiazole (0.09 mL, 0.96 mmol) with 3-*tert*-butoxycarbonyl-7-chloro-6-ethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (148mg, 0.48mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 4:1 gradient over 30 min) to give the desired intermediate (165 mg, 89%). MS (ES+) *m/z*: 389 $(M+H)^+$.

7-Chloro-6-(thiazol-2-ylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate: Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(thiazol-2-ylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (140 mg, 0.36 mmol). Elute through SCX column to give the free base of the title compound (89 mg, 86%). MS (ES+) *m/z*: 289 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound as a light yellow solid (125 mg, 86%). MS (ES+) *m/z*: 289 $(M+H)^+$.

Example 533

7-Chloro-6-pyridazin-3-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

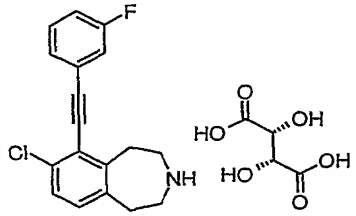


3-*tert*-Butoxycarbonyl-7-chloro-6-pyridazin-3-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 8 to couple 2-chloro-pyridazine (98 mg, 0.86 mmol) with 3-*tert*-butoxycarbonyl-7-chloro-6-ethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (104 mg, 0.34 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 4:1 gradient over 30 min) to give 3-*tert*-butoxycarbonyl-7-chloro-6-pyridazin-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (26 mg, 10 %). MS (ES+) *m/z*: 384 $(M+H)^+$.

7-Chloro-6-pyridazin-3-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-tartrate: Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-pyridazin-2-ylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-6 to give the title compound as a solid (15 mg, 51%). MS (ES+) *m/z*: 284 $(M+H)^+$.

Example 534

7-Chloro-6-(3-fluoro-phenylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



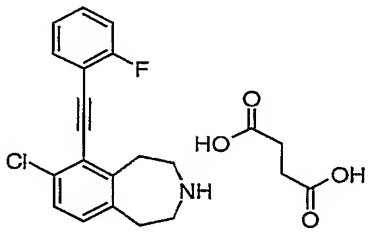
Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with (3-fluorophenyl)-ethyne (241 mg, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40

min) to give 7-chloro-6-(3-fluoro-phenylethynyl)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (247 mg, 64%). MS (ES+) *m/z*: 396 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(3-fluoro-phenylethynyl)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (68 mg, 0.18 mmol). Purify by SCX chromatography to give the free base of the title compound (46 mg, 85%). MS (ES+) *m/z*: 300 $(M+H)^+$. Use a method similar to the General Procedure 2-6 to give the title compound as a white solid (61 mg, 94%). MS (ES+) *m/z*: 300 $(M+H)^+$.

Example 535

7-Chloro-6-(2-fluoro-phenylethynyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

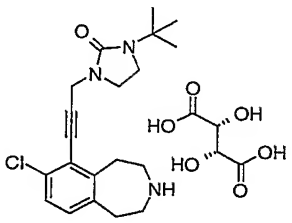


Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with (2-fluorophenyl)-ethyne (241 mg, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40 min) to give 7-chloro-6-(2-fluoro-phenylethynyl)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (262 mg, 68%). MS (ES+) *m/z*: 396 $(M+H)^+$.

Use methods similar to the General Procedures 1-1 and 2-1 to give the title compound as a white solid (93%). MS (ES+) *m/z*: 300 $(M+H)^+$.

Example 536

6-[3-(3-*tert*-Butyl-2-oxo-imidazolidin-1-yl)-prop-1-ynyl]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

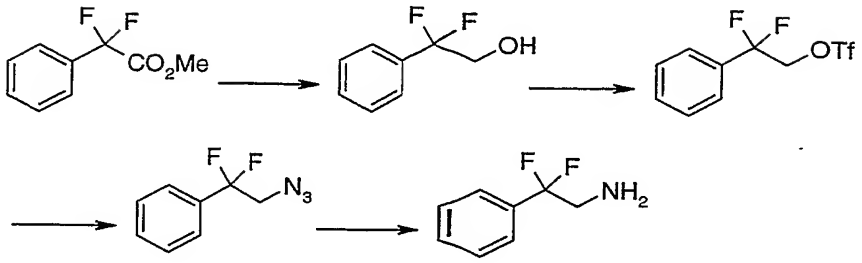


Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with 1-*tert*-butyl-3-prop-2-ynyl-imidazolidin-2-one (360 mg, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (19:1 to 3:2 gradient) to give 6-[3-(3-*tert*-butyl-2-oxo-imidazolidin-1-yl)-prop-1-ynyl]-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (380 mg, 83%) as a yellow oil. LC-MS (ES+) *m/z*: 478 $(M+Na)^+$, 456 $(M+H)^+$, t_R = 4.43 min.

Use a method similar to the General Procedure 1-1, but adding water (10 mL) to the ammonia/methanol solution (20 mL, 7N solution), to deprotect 6-[3-(3-*tert*-butyl-2-oxo-imidazolidin-1-yl)-prop-1-ynyl]-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (329 mg, 0.72 mmol) and give the free base of the title compound (217 mg, 84%). Use a method similar to the General Procedure 2-6 to give the title compound as a solid (211 mg, 58% overall yield). LC-MS (ES+) *m/z*: 360 $(M+H)^+$, t_R = 4.54 min.

Preparation 253

2,2-Difluoro-2-phenyl-ethylamine



2,2-Difluoro-2-phenyl-ethanol: Add lithium aluminum hydride (5.18 mL, 5.18 mmol, 1M solution in THF) to a solution of methyl difluorophenylethanoate (0.964 g, 5.18 mmol, prepared by following the procedure described in *J. Org. Chem.* **1995**, *60*, 5174-5179) in anhydrous THF (10 mL) at 0 °C. Stir the mixture at room temperature for 45 min. Cool to 0 °C and quench with EtOAc and then water. Separate the organic phase and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate (0.8 g, 98%) that was used without any further purification.

2,2-Difluoro-2-phenyl-ethyl trifluoromethanesulfonate: Add triflic anhydride (1.28 mL, 2.14 g) dropwise to a stirred solution of 2,2-difluoro-2-phenyl-ethanol (0.8 g, 5.06 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.556 g, 7.59 mmol) in anhydrous dichloromethane (25 mL) at -78 °C. Stir the reaction overnight while the temperature warms up. Dilute the mixture with pentane and filter the precipitate over Celite®. Concentrate the filtrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (95:5) to provide the title compound (946 mg, 64%).

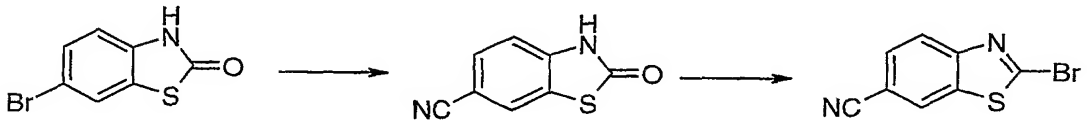
(2-Azido-1,1-difluoro-ethyl)-benzene: Heat at 60 °C a solution of 2,2-difluoro-2-phenyl-ethyl trifluoromethanesulfonate (759 mg, 2.617 mmol) and sodium azide (357 mg, 5.496 mmol) in anhydrous DMF (10 mL) under nitrogen for 3 h. Cool the reaction mixture to room temperature. Dilute with water and extract the aqueous phase twice with

diethyl ether. Wash the combined organic extracts twice with ice-cold water, dry over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as an oil (475 mg, 99%) that was used without any further purification.

2,2-Difluoro-2-phenyl-ethylamine: Dissolve (2-azido-1,1-difluoro-ethyl)-benzene (475 mg, 2.59 mmol) in EtOAc (30 mL). Add 10% Pd/C and submit the mixture to hydrogenation under atmospheric pressure (balloon) for 1 h. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo* to provide the title compound as an oil (400 mg, 98%) that was used without any further purification.

Preparation 254

2-Bromo-benzothiazole-6-carbonitrile

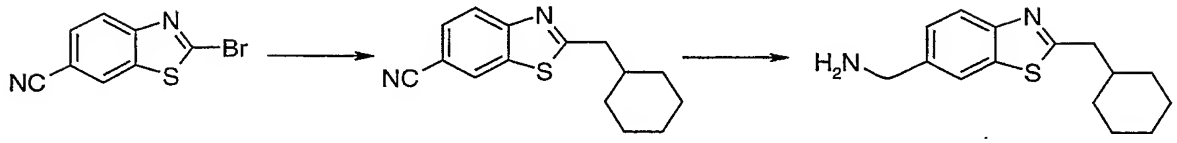


2-Oxo-2,3-dihydro-benzothiazole-6-carbonitrile: Combine 6-bromobenzothiazolinone (2 g, 8.69 mmol), copper cyanide (1.3 g, 1.48 mmol), anhydrous DMF (5 mL) and heat at reflux for 15 h. Add water (20 mL) and sodium cyanide (1.4 g, 27.7 mmol) at 100 °C. Cool the reaction mixture to room temperature and stir for 2 h. Extract the reaction mixture with EtOAc (5 x 30 mL) at 70 °C. Combine the organic layers, wash with water (3 x 40 mL) and dry over anhydrous Na_2SO_4. Concentrate *in vacuo* to obtain the desired intermediate as a yellow solid (2 g, 87%). GC-MS *m/z*: 176 (M^+).

2-Bromo-benzothiazole-6-carbonitrile: Combine 2-oxo-2,3-dihydro-benzothiazole-6-carbonitrile (1.1 g, 6.24 mmol), tetrabutylammonium bromide (3 g, 9.36 mmol), phosphorus pentoxide (2.7 g, 18.7 mmol), anhydrous toluene (40 mL) and heat at reflux for 2.5 h. Cool the reaction mixture to room temperature. Decant the toluene layer and wash with saturated aqueous $NaHCO_3$ (3 x 10 mL). Concentrate the organic phase *in vacuo* and purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 4:1 gradient) to obtain the title compound as a colorless oil (0.9 g, 61%). GC-MS *m/z*: 239 (M^+).

Preparation 255

6-Aminomethyl-2-cyclohexylmethyl-benzothiazole

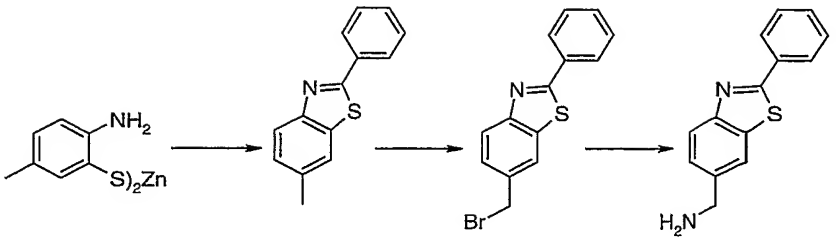


2-Cyclohexylmethyl-benzothiazole-6-carbonitrile: Place 2-bromo-benzothiazole-6-carbonitrile (0.2 g, 0.96 mmol), anhydrous THF (3 mL), 1-methyl-2-pyrrolidinone (3 mL), tetrabutylammonium iodide (1.1 g, 2.89 mmol), tris(dibenzylideneacetone)dipalladium(0) (18 mg, 0.09 mmol) and [1,1'-bis(diphenylphosphino)ferrocine]dichloropalladium (II) (11 mg, 0.09 mmol) in a flask. Add 0.5M cyclohexylmethylzinc bromide in THF (3.8 mL, 1.92 mmol) to the mixture, degas 3 times by partially evacuating the atmosphere and flushing with nitrogen and stir the reaction mixture at 80 °C for 2 h. Cool the reaction mixture to room temperature, dilute with EtOAc (10 mL) and wash with brine (10 mL). Dry the organic layer over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting sequentially with hexane/EtOAc (1:0 to 4:1 gradient) to obtain the desired intermediate as a yellow solid (140 mg, 57%). GC-MS *m/z*: 256 (M^+).

6-Aminomethyl-2-cyclohexylmethyl-benzothiazole: Dissolve 2-cyclohexylmethyl-benzothiazole-6-carbonitrile (0.2 g, 0.55 mmol) in anhydrous THF (2 mL) and add slowly 1M lithium aluminum hydride in THF (0.82 mL, 0.82 mmol) at room temperature. Stir the reaction mixture at room temperature for 0.5 h. Quench the reaction mixture with water until a granular precipitate starts to form and filter through a pad of Celite®. Evaporate the solvent and purify the residue by SCX chromatography to obtain the title compound as a yellow oil (0.1 g, 92%). MS (ES+) *m/z*: 260 $(M+H)^+$.

Preparation 256

6-Aminomethyl-2-phenyl-benzothiazole



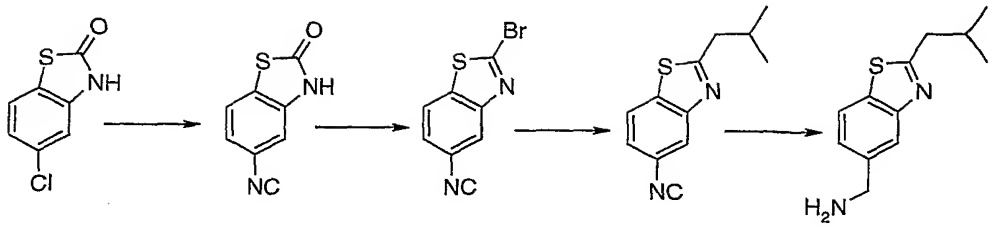
6-Methyl-2-phenyl-benzothiazole: Heat at reflux a mixture of 2-amino-5-methyl-benzenethiol zinc salt (13.5 g, 24.9 mmol, prepared by following the procedure described in *Helv. Chim. Acta* **1974**, *57*, 2664) and ethyl benzimidate hydrochloride (9.23 g, 49.7 mmol) in methanol (240 mL) for 9 h. Filter the mixture, evaporate the filtrate and purify the residue by chromatography on silica gel eluting with hexane/EtOAc (100:0 to 85:15 gradient) to obtain the desired intermediate (5.7 g, 51%). MS (EI) *m/z*: 225 (M^+).

6-Bromomethyl-2-phenyl-benzothiazole: Heat 5-methyl-2-phenyl-benzothiazole (5.7 g, 25.3 mmol) and NBS (4.73 g, 26.6 mmol) in carbon tetrachloride (140 mL) at 80 °C for 3 h. Cool the mixture, double the volume with dichloromethane, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 7:3 gradient) to obtain the desired intermediate (3.1 g, 40%). MS (EI) *m/z*: 303, 305 (M^+).

6-Aminomethyl-2-phenyl-benzothiazole: Add 6-bromomethyl-2-phenyl-benzothiazole (2 g, 6.57 mmol) as a suspension in methanol (100 mL) to 7M ammonia in methanol (400 mL) at 0 °C over 10 min and then stir for 3 h at room temperature. Concentrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with dichloromethane/methanol (1:0 to 3:1) to obtain the title compound (1.2 g, 76%). MS (ES+) *m/z*: 241 ($M+H^+$).

Preparation 257

5-Aminomethyl-2-isobutyl-benzothiazole



2-Oxo-2,3-dihydro-benzothiazole-5-carbonitrile: Heat a mixture of 5-chloro-3*H*-benzothiazol-2-one (9.3 g, 50 mmol), nickel(II) bromide (10.9 g, 50 mmol) and sodium cyanide (4.91 g, 100 mmol) in 1-methyl-pyrrolidinone (100 mL) in a microwave reactor to 200 °C over 15 min and hold 1 h. Filter the cooled mixture through a glass frit, add diethyl ether and brine and filter again. Wash the organic phase with brine three times and concentrate *in vacuo*. Pass the residue through a plug of silica gel eluting with hexane/EtOAc (2:1) and then dichloromethane/methanol (9:1) to obtain the desired intermediate (3.2 g, 36%). MS (ES+) *m/z*: 177 $(M+H)^+$.

2-Bromo-benzothiazole-5-carbonitrile: Heat 2-oxo-2,3-dihydro-benzothiazole-5-carbonitrile (3.2 g, 18.2 mmol) in toluene (120 mL) with tetrabutylammonium bromide (8.78 g, 27.2 mmol) and phosphorus pentoxide (7.73 g, 54.5 mmol) for 3 h at reflux. Cool the mixture, decant the solution from the reaction residue and partition between diethyl ether and brine. Add water and dichloromethane to the reaction residue and reflux for 20 min. Wash the dichloromethane layer with saturated aqueous $NaHCO_3$ and brine, and combine with the ether washing. Dry the organic mixture over Na_2SO_4 and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 3:7 gradient) to give the desired intermediate (0.85 g, 20%). MS (EI) *m/z*: 238, 240 (M^+).

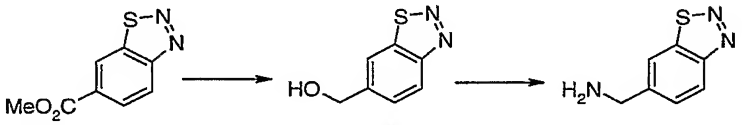
2-Isobuty-benzothiazole-5-carbonitrile: Heat 2-bromo-benzothiazole-5-carbonitrile (0.3 g, 1.26 mmol) in 1-methyl-pyrrolidinone (4.2 mL) with 2-methylpropylzinc bromide (5 mL, 2.5 mmol, 0.5M solution in THF), N-methylimidazole (0.15 g, 1.88 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (20.5 mg, 0.025 mmol) at 80 °C for 3 h. Cool the mixture and partition between diethyl ether and brine. Dry the organic layer over Na_2SO_4 and

concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 1:1 gradient) to give the desired intermediate (113 mg, 42%). MS (EI) *m/z*: 216 (M^+).

5-Aminomethyl-2-isobutyl-benzothiazole: Add lithium aluminum hydride (0.78 mL, 0.78 mmol, 1M solution in THF) to 2-isobuty-benzothiazole-5-carbonitrile (113 mg, 0.52 mmol) in THF (5 mL) and stir for 4 h at room temperature. Add water (0.27 mL), 2N sodium hydroxide (0.27 mL) and water (0.37 mL). Filter the precipitate and wash the filtrate with brine. Dry over Na_2SO_4 and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:1) and then 1M ammonia in methanol/dichloromethane (1:9). Purify the polar fraction by SCX chromatography to give the title compound (63 mg, 55%). MS (ES+) *m/z*: 221 ($M+H^+$).

Preparation 258

6-Aminomethyl-benzo[1,2,3]thiadiazole

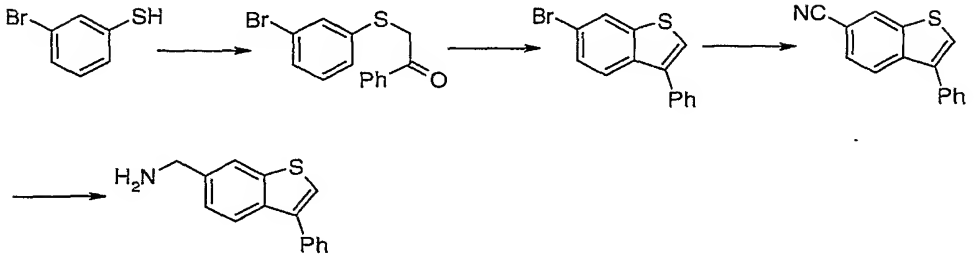


6-Hydroxymethyl-benzo[1,2,3]thiadiazole: Add sodium borohydride (1.35 g, 36 mmol) in five portions over 4 h to a solution of benzo[1,2,3]thiadiazole-6-carboxylic acid methyl ester (0.35 g, 1.8 mmol, prepared by following the procedure described in *J. Heterocyclic Chem.* **1972**, 1149) in methanol (18 mL) at 0 °C. Add acetone to quench and evaporate the mixture onto silica gel. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 2:3 gradient) to give the desired intermediate (133 mg, 45%). MS (GCMS) *m/z*: 166 M^+.

6-Aminomethyl-benzo[1,2,3]thiadiazole: Stir 6-hydroxymethyl-benzo[1,2,3]thiadiazole (133 mg, 0.8 mmol) in thionylchloride (5 mL) for 3 h at room temperature. Evaporate the mixture then add 7M ammonia in methanol (10 mL) and stir at room temperature in a sealed tube for 48 h. Evaporate the mixture and purify the residue by SCX chromatography to give the title compound (115 mg, 87%). MS (ES+) *m/z*: 166 $(M+H)^+$.

Preparation 259

6-Aminomethyl-3-phenyl-benzothiophene



2-(3-Bromo-phenylthio)-1-phenyl-ethanone: Add potassium hydroxide (4.89 g, 87.3 mmol) and 2-bromoacetophenone (15.8 g, 79.3 mmol) to a solution of 3-bromobenzenethiol (15 g, 79.3 mmol) in ethanol (200 mL, 70% in water) at 0 °C. After stirring 16 h, add water to precipitate a yellow solid. Filter to obtain the desired intermediate (24.6 g, 100%).

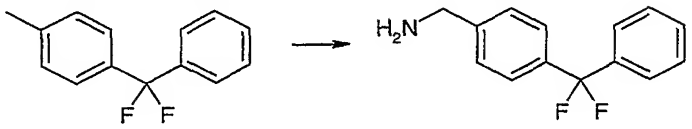
6-Bromo-3-phenylbenzothiophene: Heat 2-(3-bromo-phenylthio)-1-phenyl-ethanone (4 g, 13 mmol) in polyphosphoric acid (4 g) at 80 °C for 4 h. Add EtOAc and water to the mixture and wash with saturated aqueous $NaHCO_3$ and brine. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Slurry the residue in hexane and purify by chromatography on silica gel eluting with hexane to give the desired intermediate that is used without further purification (2.7 g, 72%). MS (GCMS) *m/z*: 289 M^+.

6-Cyano-3-phenylbenzothiophene: Combine 6-bromo-3-phenylbenzothiophene (0.5 g, 1.73 mmol) and copper cyanide (0.56 g, 6.23 mmol) and reflux 3 h in 1-methyl-2-pyrrolidinone (1.73 mL). Add ferric chloride (2.11 g, 7.79 mmol) in concentrated HCl (1.73 mL) and stir 1.5 h. Cool the mixture and partition between diethyl ether and brine. Dry the organic layer over Na_2SO_4, filter and evaporate onto silica gel. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 3:2 gradient) to give the desired intermediate that is used without further purification (0.27 g, 67%). MS (GCMS) *m/z*: 235 M^+.

6-Aminomethyl-3-phenyl-benzothiophene: Dissolve 6-cyano-3-phenylbenzothiophene (0.27 g, 1.16 mmol) in anhydrous THF (6 mL) and add lithium aluminum hydride (3.45 mL, 1M solution in THF) at 0 °C. After 2 h, add water (0.86 mL), 2N aqueous NaOH (0.86 mL) and water (1.24 mL). Filter off the solids and evaporate the residue. Purify by prep HPLC (Zorbax SB-Phenyl column 21.2 x 250 mm, 5% to 50% acetonitrile in 0.1% TFA-water solution) and obtain the free base by SCX chromatography to give the title compound that is used without further purification (187 mg, 68%). MS (ES+) *m/z*: 223 $(M-NH_2)^+$.

Preparation 260

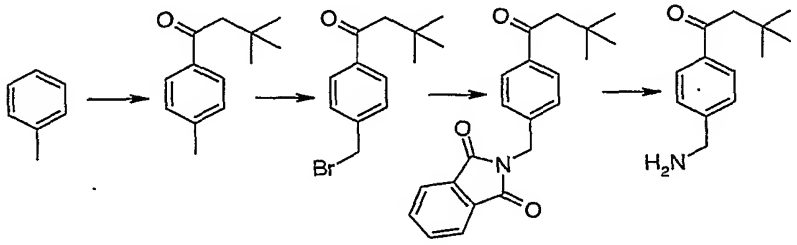
4-(Difluoro-phenyl-methyl)-benzylamine



Combine 4-(difluoro-phenyl-methyl)-toluene (0.29 g, 1.35 mmol, prepared by following the procedure described in *Tetrahedron* **1996**, *52*, 9), NBS (0.26 g, 1.48 mmol), and AIBN (6 mg, 0.03 mmol) in carbon tetrachloride (8 mL) and heat at 80 °C for 16 h. Evaporate the mixture and pass the residue through a pad of silica gel washing with hexane and evaporate the filtrate. Dissolve the residue in methanol and add dropwise to 7M ammonia in methanol (100 mL) at 0 °C. After 4.5 h, evaporate the mixture and isolate the amine by SCX chromatography (0.1 g, 32%). MS (ES+) *m/z*: 234 $(M+H)^+$.

Preparation 261

4-(3,3-Dimethyl-butyryl)-benzylamine



3,3,4'-Trimethylbutyrophenone: Add slowly *tert*-butylacetyl chloride (2 g, 14.858 mmol) to an ice-cold stirred solution of aluminum trichloride (2.972 g, 22.28 mmol) in

anhydrous toluene (40 mL). Stir the reaction mixture at ambient temperature overnight. Add slowly ice-cold water and extract the mixture twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (2.82 g, 100%) that was used without any further purification. GC-MS *m/z*: 190 (M^+).

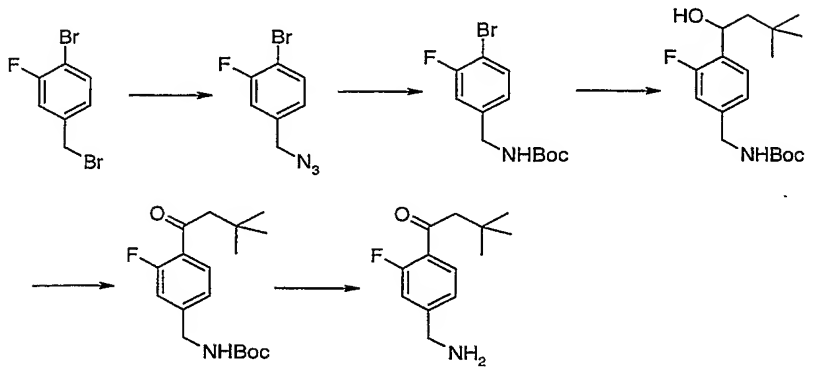
4-(3,3-Dimethyl-butyryl)-benzyl bromide: Heat a mixture of 3,3,4'-trimethylbutyrophenone (2 g, 10.52 mmol), NBS (2.061 g, 11.57 mmol), and AIBN (43 mg, 0.263 mmol) in carbon tetrachloride (60 mL) for 14 h at reflux. Cool the reaction mixture to ambient temperature and wash sequentially with water, 1M aqueous HCl, 5% aqueous $NaHCO_3$ and brine. Concentrate the organic layer *in vacuo* to provide the desired intermediate as oil (2.54 g, 90%) that was used without any further purification.

2-[4-(3,3-Dimethyl-butyryl)-benzyl]-isoindole-1,3-dione: Add 4-(3,3-dimethyl-butyryl)-benzyl bromide (1 g, 3.731 mmol) to a stirred suspension of potassium phthalimide (0.705 g, 3.805 mmol) in anhydrous DMF (20 mL). Stir the mixture overnight at room temperature. Dilute with EtOAc and wash twice with ice-cold water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (19:1, 4:1) to provide the desired intermediate as oil (1.24 g, 100%).

4-(3,3-Dimethyl-butyryl)-benzylamine: Add hydrazine hydrate (0.189 mL, 3.913 mmol) to a stirred suspension of 2-[4-(3,3-dmethyl-butyryl)-benzyl]-isoindole-1,3-dione (875 mg, 2.609 mmol) in methanol (15 mL). Heat the mixture to reflux overnight. Cool the mixture to room temperature and concentrate *in vacuo*. Partition the residue between EtOAc and 5N aqueous HCl and wash the acidic aqueous phase again with 5N aqueous HCl. Basify with 5N aqueous NaOH to pH 12. Extract the basic aqueous solution three times with chloroform. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the title compound as a yellow oil (411 mg, 77%) that was used without any further purification.

Preparation 262

4-(3,3-Dimethyl-butyryl)-3-fluoro-benzylamine



4-Azidomethyl-1-bromo-2-fluoro-benzene: Add sodium azide (2.912 g, 44.8 mmol) to a solution of 4-bromo-3-fluorobenzyl bromide (6 g, 22.4 mmol) in anhydrous DMF (127 mL) at room temperature under nitrogen. Heat the mixture at 90 °C for 1 h. Concentrate *in vacuo* and partition the residue between water and EtOAc. Extract the aqueous phase twice with EtOAc. Wash the combined organics extracts with iced-water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate as a solid (4.92 g, 96%).

4-Bromo-*N*-(*tert*-butoxycarbonyl)-3-fluoro-benzylamine: Add 10% Pd/C (492 mg) and di-*tert*-butyl-dicarbonate (4.668 g, 21.4 mmol) to a solution of 4-azidomethyl-1-bromo-2-fluoro-benzene (4.92 g, 21.4 mmol) in ethanol (90 mL) and submit the mixture to hydrogenation at atmospheric pressure overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to obtain the desired intermediate as a solid (1.55 g, 25%).

***N*-(*tert*-Butoxycarbonyl)-3-fluoro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine:** Add butyllithium (7.3 mL, 11.7 mmol) to a solution of 4-bromo-*N*-(*tert*-butoxycarbonyl)-3-fluoro-benzylamine (1.55 g, 5.1 mmol) in diethyl ether (54 mL) at –78 °C under nitrogen and stir for 30 min. Add 3,3-dimethylbutyraldehyde (562 mg, 0.7 mL, 5.6 mmol), stir for 30 min at –78 °C and then warm to room temperature. Add water and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over

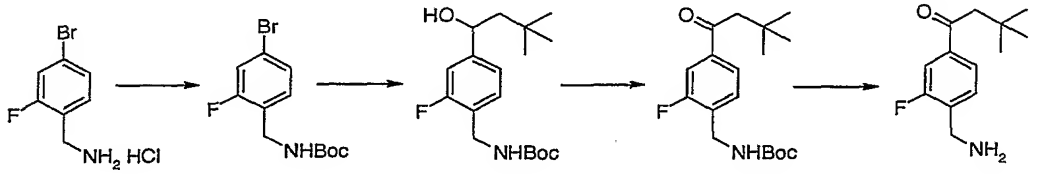
Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to obtain the desired intermediate as a yellow oil (394 mg, 24%).

N-(*tert*-Butoxycarbonyl)-4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamine: Add manganese dioxide (1.132 g, 13 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-3-fluoro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine (283 mg, 0.87 mmol) in anhydrous 1,4-dioxane (11.5 mL) at room temperature. Heat the reaction mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate as an oil (216 mg, 77%).

4-(3,3-Dimethyl-butyryl)-3-fluoro-benzylamine: Add 4N hydrogen chloride in dioxane (2.7 mL, 10.8 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamine (296 mg, 0.92 mmol) in dichloromethane (11 mL) and stir for 4 h. Concentrate *in vacuo* and wash the solid obtained with diethyl ether. Suspend the solid in saturated aqueous $NaHCO_3$ and stir for 30 min. Extract twice with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as an oil (175 mg, 82%).

Preparation 263

4-(3,3-Dimethyl-butyryl)-2-fluoro-benzylamine



4-Bromo-*N*-(*tert*-butoxycarbonyl)-2-fluoro-benzylamine: Add triethylamine (6.334 g, 8.8 mL, 52.6 mmol) and di-*tert*-butyl-dicarbonate (4.54 g, 20.8 mmol) to a solution of 4-bromo-2-fluoro-benzylamine hydrochloride (5 g, 20.8 mmol) in dichloromethane (254 mL) and stir overnight. Wash the organic layer with water and then extract back the aqueous phase with dichloromethane. Dry the combined organic extracts over Na_2SO_4,

filter and concentrate *in vacuo* to obtain the desired intermediate as a white solid (6.11 g, 97%).

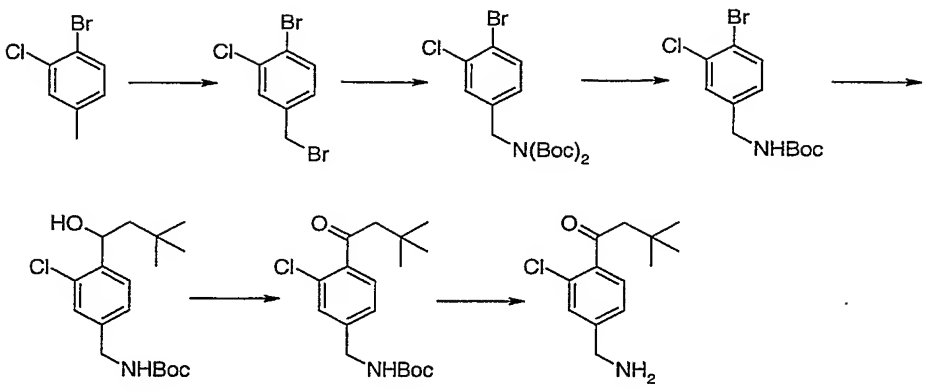
N-(*tert*-Butoxycarbonyl)-2-fluoro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine: Add butyllithium (14.2 mL, 22.7 mmol) to a solution of 4-bromo-*N*-(*tert*-butoxycarbonyl)-2-fluoro-benzylamine (3 g, 9.9 mmol) in diethyl ether (105 mL) at –78 °C under nitrogen and stir for 30 min. Add 3,3-dimethylbutyraldehyde (1.086 g, 1.4 mL, 10.8 mmol), stir for 30 min at –78 °C and then warm to room temperature. Add water and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to obtain the desired intermediate as a yellow oil (1.179 g, 37%).

N-(*tert*-Butoxycarbonyl)-4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamine: Add manganese dioxide (4.4 g, 50.6 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-2-fluoro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine (1.1 g, 3.38 mmol) in anhydrous 1,4-dioxane (45 mL) at room temperature. Heat the reaction mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain the desired intermediate as an oil (980 mg, 90%).

4-(3,3-Dimethyl-butyryl)-2-fluoro-benzylamine: Add 4N hydrogen chloride in dioxane (5.5 mL, 22 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamine (600 mg, 1.85 mmol) in dichloromethane (22 mL) and stir for 6.5 h. Concentrate *in vacuo* and wash the solid obtained with diethyl ether. Suspend the solid into saturated aqueous $NaHCO_3$ and stir for 30 min. Extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as an oil (420 mg, 99%).

Preparation 264

3-Chloro-4-(3,3-dimethyl-butyryl)-benzylamine



4-Bromo-3-chloro-benzyl bromide: Add NBS (5.266 g, 23.9 mmol) and benzoyl peroxide (49 mg, 0.2 mmol) to a solution of 4-bromo-3-chlorotoluene (4.925 g, 23.9 mmol) in carbon tetrachloride (49 mL) and heat overnight at 90 °C. Cool to 0 °C and filter the mixture. Concentrate the filtrate *in vacuo* to obtain the desired intermediate as a yellow oil (5.807 g, 85%).

4-Bromo-3-chloro-*N*-(di-*tert*-butoxycarbonyl)-benzylamine: Add sodium hydride (382 mg, 15.9 mmol) to a solution of di-*tert*-butyl-iminodicarboxylate (2.533 g, 11.7 mmol) in anhydrous DMF (15 mL) at room temperature under nitrogen and stir for 15 min. Then add a solution of 4-bromo-3-chloro-benzyl bromide (3 g, 10.6 mmol) in anhydrous DMF (5 mL) and stir for 1 h. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts with iced-water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate (2.783 g, 62%).

4-Bromo-3-chloro-*N*-(*tert*-butoxycarbonyl)-benzylamine: Add a solution of sodium hydroxide (264 mg, 6.6 mmol) in methanol (23.5 mL) to a solution of 4-bromo-3-chloro-*N*-(di-*tert*-butoxycarbonyl)-benzylamine (2.783 g, 6.6 mmol) in THF (11.7 mL) and stir overnight. Concentrate *in vacuo*. Add water and filter the precipitate formed to obtain the desired intermediate as a white solid (1.823 g, 86%).

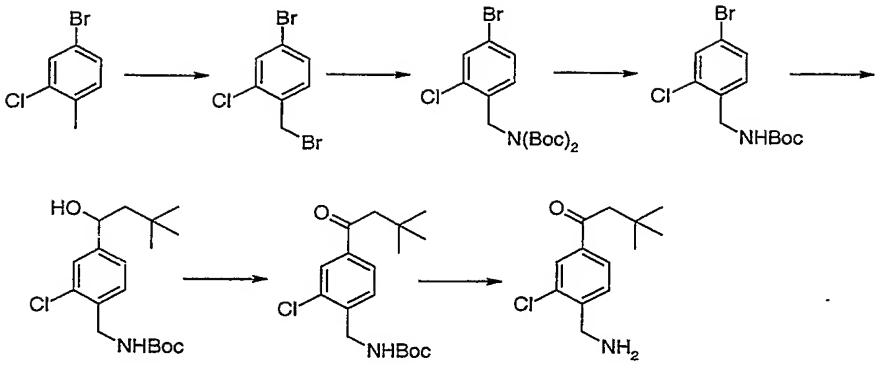
***N*-(*tert*-Butoxycarbonyl)-3-chloro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine:** Add butyllithium (8.2 mL, 13.1 mmol) to a solution of 4-bromo-3-chloro-*N*-(*tert*-butoxycarbonyl)-benzylamine (1.823 g, 5.7 mmol) in diethyl ether (46 mL) at –78 °C under nitrogen and stir for 30 min. Add 3,3-dimethylbutyraldehyde (1.427 g, 1.7 mL, 14.3 mmol), stir for 30 min at –78 °C and then warm to room temperature. Add water and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate as a yellow oil (274 mg, 14%).

***N*-(*tert*-Butoxycarbonyl)-3-chloro-4-(3,3-dimethyl-butyryl)-benzylamine:** Add manganese dioxide (1.096 g, 12.6 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-3-chloro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine (274 mg, 0.8 mmol) in anhydrous 1,4-dioxane (11.5 mL) at room temperature. Heat the mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate as a yellow oil (175 mg, 64%).

3-Chloro-4-(3,3-dimethyl-butyryl)-benzylamine: Add 4N hydrogen chloride in dioxane (0.9 mL, 3.6 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-3-chloro-4-(3,3-dimethyl-butyryl)-benzylamine (100 mg, 0.3 mmol) in dichloromethane (6 mL) and stir overnight. Concentrate *in vacuo* and wash the solid obtained with diethyl ether. Suspend the solid into saturated aqueous $NaHCO_3$ and stir for 30 min. Extract twice with dichoromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as a yellow oil (66 mg, 92%).

Preparation 265

2-Chloro-4-(3,3-dimethyl-butyryl)-benzylamine



4-Bromo-2-chloro-benzyl bromide: Add NBS (13.171 g, 74 mmol) and benzoyl peroxide (152 mg, 0.63 mmol) to a solution of 4-bromo-2-chlorotoluene (15.2 g, 74 mmol) in carbon tetrachloride (152 mL) and stir for 6 days at 90 °C. Cool to 0 °C, filter the mixture and concentrate the filtrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (99:1) to obtain the desired intermediate as a yellow oil (12.7 g, 61%).

4-Bromo-2-chloro-*N*-di-(*tert*-butoxycarbonyl)-benzylamine: Add sodium hydride (382 mg, 15.9 mmol) to a solution of di-*tert*-butyl-iminodicarboxylate (2.533 g, 11.7 mmol) in anhydrous DMF (15 mL) at room temperature under nitrogen and stir for 15 min. Then add a solution of 4-bromo-2-chloro-benzyl bromide (3 g, 10.6 mmol) in anhydrous DMF (5 mL) and stir for 1 h. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts with iced-water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (4:1) to obtain the desired intermediate (4.2 g, 94%).

4-Bromo-*N*-(*tert*-butoxycarbonyl)-2-chloro-benzylamine: Add a solution of sodium hydroxide (399 mg, 9.98 mmol) in methanol (35.5 mL) to a solution of 4-bromo-2-chloro-*N*-di-(*tert*-butoxycarbonyl)-benzylamine (4.2 g, 9.98 mmol) in THF (17.7 mL) and stir overnight. Concentrate *in vacuo* and partition the residue between water and EtOAc. Extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in* vacuo. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to obtain the desired intermediate (2.625 g, 82%).

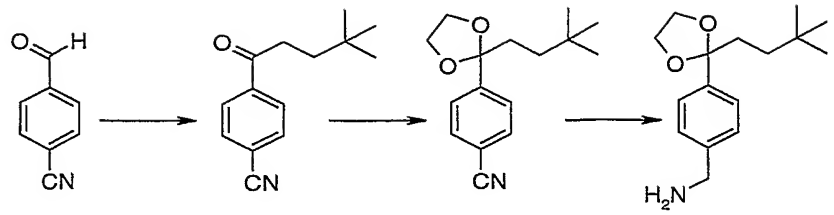
***N*-(*tert*-Butoxycarbonyl)-2-chloro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine:** Add butyllithium (11.7 mL, 18.65 mmol) to a solution of 4-bromo-*N*-(*tert*-butoxycarbonyl)-2-chloro-benzylamine (2.601 g, 8.11 mmol) in diethyl ether (86 mL) at –78 °C under nitrogen and stir for 2 h. Add 3,3-dimethylbutyraldehyde (1.868 g, 2.3 mL, 18.65 mmol), stir for 30 min at –78 °C and then warm to room temperature. Add water and extract twice the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting hexane/EtOAc (85:15) to obtain the desired intermediate as a yellow oil (1.825 mg, 66%).

***N*-(*tert*-Butoxycarbonyl)-2-chloro-4-(3,3-dimethyl-butyryl)-benzylamine:** Add manganese dioxide (7.276 g, 83.7 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-2-chloro-4-(1-hydroxy-3,3-dimethyl-butyl)-benzylamine (1.819 g, 5.3 mmol) in anhydrous 1,4-dioxane (75 mL) at room temperature. Heat the mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to obtain the desired intermediate as a yellow oil (1.362 g, 76%).

2-Chloro-4-(3,3-dimethyl-butyryl)-benzylamine: Add 4N hydrogen chloride in dioxane (6 mL, 24 mmol) to a solution of *N*-(*tert*-butoxycarbonyl)-2-chloro-4-(3,3-dimethyl-butyryl)-benzylamine (700 mg, 2.06 mmol) in dichloromethane (25 mL) and stir overnight. Concentrate *in vacuo* and wash the solid obtained with diethyl ether. Suspend the solid into saturated aqueous $NaHCO_3$ and stir for 30 min. Extract twice with dichoromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as a yellow oil (477 mg, 97%).

Preparation 266

4-[2-(3,3-Dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine



4-(4,4-Dimethyl-pentanoyl)-benzonitrile: Keep Mg turnings (402 mg, 15.251 mmol) *in vacuo* in a two-neck round bottom flask for 2 h. Purge the flask with nitrogen/vacuo several times. Add a couple crystals of iodine, anhydrous THF (60 mL) and 3,3-dimethyl-bromobutane (0.8 mL, 5.59 mmol) slowly (exothermic reaction observed). Add dropwise the remaining 3,3-dimethyl-bromobutane (1.6 mL, 11.18 mmol) and reflux the mixture overnight. Add some additional 3,3-dimethyl-bromobutane (0.24 mL, 1.67 mmol) and reflux for 30 min. Cool the mixture to –10 °C and add a solution of 4-cyanobenzaldehyde (4 g, 30.502 mmol) in anhydrous THF (40 mL). Warm the flask gradually to room temperature overnight. Quench the mixture with 0.1M aqueous HCl (100 mL) and extract twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1) to give the desired intermediate as an oil (0.752 g, 23%).

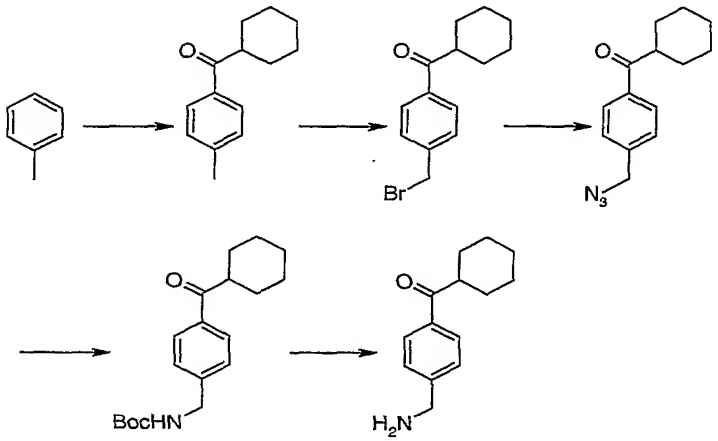
4-[2-(3,3-Dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzonitrile: Dissolve 4-(4,4-dimethyl-pentanoyl)-benzonitrile (275 mg, 1.28 mmol) in toluene (10 mL). Add ethylene glycol (0.35 mL, 6.4 mmol) and p-toluenesulfonic acid monohydrate (24 mg, 0.128 mmol). Heat the mixture at 135 °C in a Dean-Stark for 2 h and then at 120 °C overnight. Cool the mixture to room temperature, dilute with EtOAc ans wash with saturated aqueous $NaHCO_3$. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on basic alumina eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as an oil (0.272 g, 82%).

4-[2-(3,3-Dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine: Dissolve 4-[2-(3,3-dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzonitrile (271 mg, 1.046 mmol) in anhydrous THF (10 mL). Add under nitrogen 1M lithium aluminum hydride in THF (2.1 mL, 2.1

mmol) at 0 °C and stir the mixture at room temperature for 2 h. Cool to 0 °C, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to obtain the desired intermediate as an oil (0.263 mg) that was used without any further purification.

Preparation 267

4-Cyclohexanecarbonyl-benzylamine



Cyclohexyl-*p*-tolyl-methanone: Dissolve cyclohexanecarbonyl chloride (2 g, 13.6 mmol) in anhydrous toluene (30 mL). Cool the solution to 0 °C, add aluminum trichloride (2.72 g, 20.46 mmol) in three portions and stir the reaction mixture at ambient temperature overnight. Cool to 0 °C, add slowly water and extract the mixture with EtOAc. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate (2.75 g, 100%).

4-(Cyclohexanecarbonyl)-benzyl bromide: Heat a mixture of cyclohexyl-*p*-tolyl-methanone (1 g, 4.943 mmol), NBS (1.232 g, 6.92 mmol), and AIBN (41 mg, 0.247 mmol) in carbon tetrachloride (80 mL) for 14 h at reflux. Add additional NBS (264 mg) and AIBN (19 mg) and reflux the mixture for 4 h. Cool the reaction mixture to ambient temperature and filter. Concentrate the filtrate *in vacuo* to provide the desired intermediate as oil (1.132 g, 81%) that was used without any further purification.

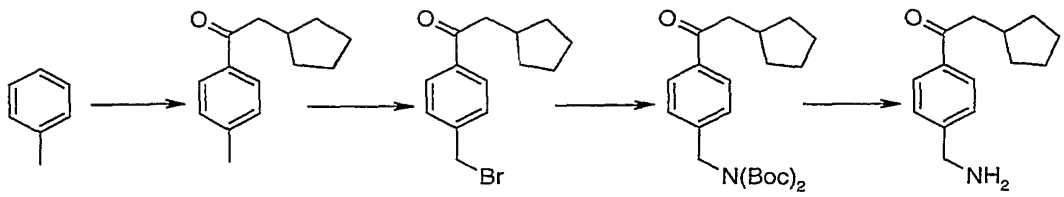
(4-Azidomethyl-phenyl)-cyclohexyl-methanone: Add sodium azide (441 mg, 6.785 mmol) to a stirred solution of 4-(cyclohexanecarbonyl)-benzyl bromide (954 mg, 3.393 mmol) in anhydrous DMF (20 mL) and heat the mixture to 90 °C for 2 h. Cool the mixture to room temperature, add water and extract the aqueous solution with diethyl ether. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as oil (310 mg, 38%).

***N*-(*tert*-Butoxycarbonyl)-4-cyclohexanecarbonyl-benzylamine:** Add 10% Pd/C (100 mg) to a solution of (4-azidomethyl-phenyl)-cyclohexyl-methanone (310 mg, 1,274 mmol) and di-*tert*-butyl-dicarbonate (278 mg, 1274 mmol) in ethanol (5 mL). Submit the mixture to hydrogenation under atmospheric pressure (balloon) for 1 h. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (92:8) to provide the desired intermediate as a white solid (197 mg, 49%).

4-Cyclohexanecarbonyl-benzylamine: Add 4N hydrogen chloride in dioxane (1 mL) to a stirred solution of *N*-(*tert*-butoxycarbonyl)-4-cyclohexanecarbonyl-benzylamine (197 mg, 0.621 mmol) in anhydrous dichloromethane (4 mL) and stir the mixture at ambient temperature for 16 h. Concentrate *in vacuo* and partition the residue between dichloromethane and saturated aqueous $NaHCO_3$. Extract the aqueous phase twice with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the title compound (125 mg, 93%) that was used without any further purification. MS (ES+) *m/z*: 218 $(M+H)^+$.

Preparation 268

4-(2-Cyclopentyl-acetyl)-benzylamine



2-Cyclopentyl-1-*p*-tolyl-ethanone: Add aluminum trichloride (2.719 g, 20.4 mmol) in three portions to a solution of cyclopentylacetyl chloride (2 g, 13.6 mmol) in anhydrous toluene (30 mL) at 0 °C. Stir the solution at room temperature overnight. Cool to 0 °C, add water and extract the aqueous phase with EtOAc. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as an oil (2.5 g, 91%).

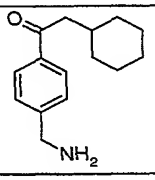
1-(4-Bromomethyl-phenyl)-2-cyclopentyl-ethanone: Add NBS (523 mg, 2.94 mmol) and AIBN (44 mg, 0.267 mmol) to a solution of 2-cyclopentyl-1-*p*-tolyl-ethanone (540 mg, 2.67 mmol) in carbon tetrachloride (80 mL) and heat overnight at 85 °C. Add water and extract the aqueous phase with dichloromethane. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (98:2, 95:5) to obtain the desired intermediate as an oil (479 mg, 64%).

***N*-Di-(*tert*-butoxycarbonyl)-4-(2-cyclopentyl-acetyl)-benzylamine:** Add sodium hydride (42 mg, 1.65 mmol) to a solution of di-*tert*-butyl-iminodicarboxylate (262 mg, 1.21 mmol) in anhydrous DMF (5 mL) at room temperature under nitrogen and stir for 5 min. Then add a solution of 1-(4-bromomethyl-phenyl)-2-cyclopentyl-ethanone (310 mg, 1.1 mmol) in anhydrous DMF (15 mL) and stir for 1 h. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts with iced-water. Dry the organic layer over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1) to obtain the desired intermediate (360 mg, 78%).

4-(2-Cyclopentyl-acetyl)-benzylamine: Add 4N hydrogen chloride in dioxane (15 mL) to a solution of *N*-di-(*tert*-butoxycarbonyl)-4-(2-cyclopentyl-acetyl)-benzylamine (300 mg, 0.72 mmol) in EtOAc (20 mL) and stir overnight. Concentrate *in vacuo*, suspend the solid obtained in diethyl ether and add hexane. Filter and wash the solid with hexane. Suspend the solid into dichloromethane, add saturated aqueous $NaHCO_3$ and stir until both phases are clear (15 min). Extract the aqueous phase with dichoromethane and EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to obtain the title compound as an oil that was used without any further purification.

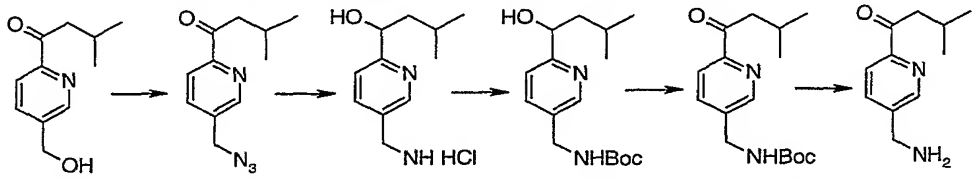
Preparation 268

The compound of Preparation 269 may be prepared essentially as described in Preparation 268 by using cyclohexylacetyl chloride. Overall yield and MS (ES+) data are shown in the Table below.

Prep.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
269		4-(2-Cyclohexyl-acetyl)-benzylamine	40	232 $(M+H)^+$

Preparation 270

5-Aminomethyl-2-(3-methyl-butyryl)-pyridine



5-Azidomethyl-2-(3-methyl-butyryl)-pyridine: Add DBU (240 mg, 1.55 mmol) to a solution of 5-hydroxymethyl-2-(3-methyl-butyryl)-pyridine (250 mg, 1.29 mmol) and diphenylphosphorylazide (430 mg, 1.55 mmol) in anhydrous toluene (10 mL) at 0 °C. Stir at 0 °C for 30 min, warm to room temperature and stir for 4 h. Dilute with EtOAc and water. Extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by

chromatography on silica gel eluting with hexane and hexane/EtOAc (9:1) to provide the desired intermediate (300 mg, 99%). MS (ES+) *m/z*: 219 $(M+H)^+$.

5-Aminomethyl-2-(1-hydroxy-3-methyl-butyl)-pyridine hydrochloride: Add 10% Pd/C (20 mg) to a solution of 5-azidomethyl-2-(3-methyl-butyryl)-pyridine (80 mg, 0.367 mmol) in ethanol (10 mL) containing concentrated HCl (1 mL). Submit the mixture to hydrogenation at atmospheric pressure for 2 h. Filter the reaction mixture over Celite® and concentrate *in vacuo* to afford the desired intermediate (95 mg, 98%). MS (ES+) *m/z*: 195 $(M+H)^+$.

5-*tert*-Butoxycarbonylaminomethyl-2-(1-hydroxy-3-methyl-butyl)-pyridine: Add di-*tert*-butyl-dicarbonate (78 mg, 0.356 mmol) and triethylamine (0.149 mL, 1.068 mmol) to a solution of 5-aminomethyl-2-(1-hydroxy-3-methyl-butyl)-pyridine hydrochloride (95 mg, 0.356 mmol) in anhydrous dichloromethane (5 mL). Stir the solution at room temperature for 3 h. Dilute the reaction mixture with dichloromethane and wash with water. Extract the aqueous phase with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (4:1) to afford the desired intermediate (60 mg, 59%).

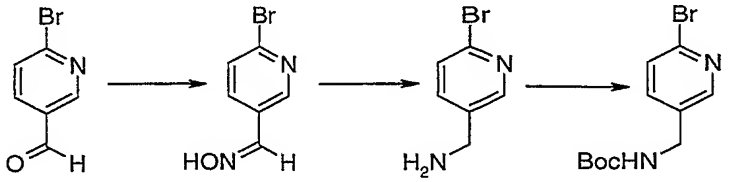
5-*tert*-Butoxycarbonylaminomethyl-2-(3-methyl-butyryl)-pyridine: Add manganese dioxide (240 mg) to a solution of 5-*tert*-butoxycarbonylaminomethyl-2-(1-hydroxy-3-methyl-butyl)-pyridine (60 mg, 0.2 mmol) in anhydrous 1,4-dioxane (1 mL) at room temperature. Heat the reaction mixture at 70 °C for 2 h. Filter the reaction mixture over Celite® and concentrate *in vacuo* to afford the desired intermediate (60 mg, 99%).

5-Aminomethyl-2-(3-methyl-butyryl)-pyridine: Add 4N hydrogen chloride in dioxane (0.5 mL) to a solution of 5-*tert*-butoxycarbonylaminomethyl-2-(3-methyl-butyryl)-pyridine (60 mg, 0.2 mmol) in anhydrous dichloromethane (2 mL) and stir the solution overnight. Concentrate *in vacuo* and partition the residue between saturated aqueous $NaHCO_3$ and dichloromethane. Extract the aqueous phase with dichloromethane (2 x 15

mL) and EtOAc (2 x 15 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound (37 mg, 95%) that was used without any further purification.

Preparation 271

2-Bromo-5-*tert*-butoxycarbonylaminomethyl-pyridine



2-Bromo-pyridine-5-carbaldehyde oxime: Add hydroxylamine hydrochloride (1.494 g, 21.504 mmol) and a solution of $NaHCO_3$ (2.71 g, 32.256 mmol) in water (15 mL) to a solution of 2-bromo-5-formyl-pyridine (2 g, 10.752 mmol, prepared by following the procedure described in *J. Org. Chem.* **2004**, *69*, 250-262) in absolute ethanol (100 mL). Stir the mixture at room temperature for 2 h. Concentrate *in vacuo* and partition the residue between EtOAc and water. Extract the aqueous phase with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (9:1, 4:1) to afford the desired intermediate as a solid (1.362 g, 63%).

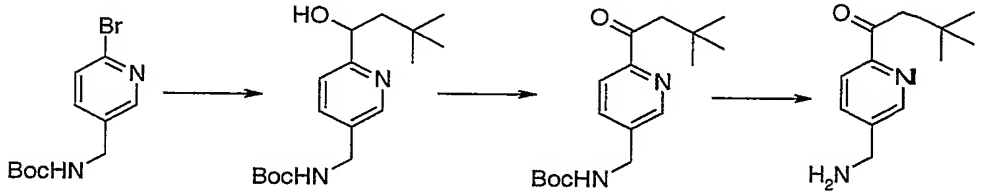
5-Aminomethyl-2-bromo-pyridine: Add dropwise a solution of 2-bromo-pyridine-5-carbaldehyde oxime (0.5 g, 2.487 mmol) in DME (10 mL) to a solution of titanium(IV) chloride (0.573 mL, 5.223 mmol) and sodium borohydride (395 mg, 10.445 mmol) in DME (20 mL) at 0 °C. Allow the mixture to warm to room temperature and stir for 3 h. Add water and remove the solvent *in vacuo*. Basify the mixture to pH 12 with 1N aqueous NaOH and extract with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to afford the desired intermediate (340 mg, 73%) that was used without further purification.

2-Bromo-5-*tert*-butoxycarbonylaminomethyl-pyridine: Add di-*tert*-butyl-dicarbonate (397 mg, 1.818 mmol) and triethylamine (0.507 mL, 3.636 mmol) to a solution of 5-

aminomethyl-2-bromo-pyridine (340 mg, 1.818 mmol) in anhydrous dichloromethane (15 mL). Stir the solution overnight at room temperature. Dilute the reaction mixture with dichloromethane and wash with water. Extract the aqueous phase with dichloromethane. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (4:1) to afford the title compound as a solid (322 mg, 62%).

Preparation 272

5-Aminomethyl-2-(3,3-dimethyl-butyryl)-pyridine



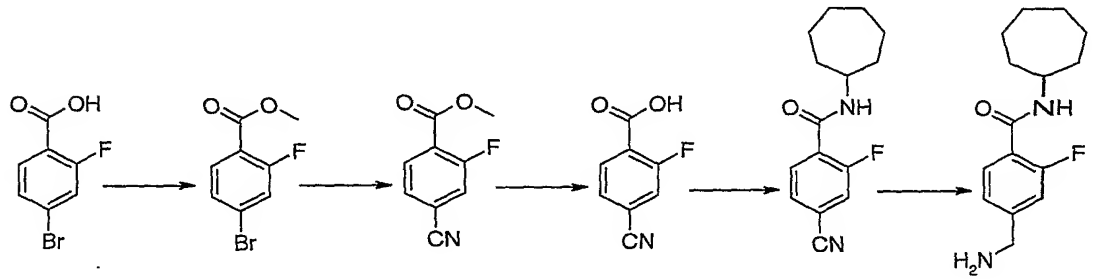
5-*tert*-Butoxycarbonylaminomethyl-2-(1-hydroxy-3,3-dimethyl-butyl)-pyridine: Add slowly butyllithium (1.088 mL, 1.741 mmol, 1.6M solution in hexane) to a solution of 2-bromo-5-*tert*-butoxycarbonylaminomethyl-pyridine (200 mg, 0.696 mmol) in anhydrous THF (10 mL) at –78 °C. Stir the mixture at this temperature for 35 min. Add 3,3-dimethylbutyraldehyde (0.219 mL, 1.741 mmol) and stir the mixture at –78 °C for 3 h. Quench the reaction mixture at –78 °C with brine. Extract the aqueous phase with EtOAc (3 x 15 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (3:2) to afford the desired intermediate as a colorless oil (118 mg, 55%). MS (ES+) *m/z*: 309 $(M+H)^+$.

5-*tert*-Butoxycarbonylaminomethyl-2-(3,3-dimethyl-butyryl)-pyridine: Add manganese dioxide (472 mg, 5.429 mmol) to a solution of 5-*tert*-butoxycarbonylaminomethyl-2-(1-hydroxy-3,3-dimethyl-butyl)-pyridine (118 mg, 0.383 mmol) in anhydrous 1,4-dioxane (5 mL) at room temperature. Heat the reaction mixture at 70 °C overnight. Filter the reaction mixture over Celite® and concentrate *in vacuo* to obtain the desired intermediate (104 mg, 89%).

5-Aminomethyl-2-(3,3-dimethyl-butyryl)-pyridine: Add 4N hydrogen chloride in dioxane (1 mL) to a solution of 5-*tert*-butoxycarbonylaminomethyl-2-(3,3-dimethyl-butyryl)-pyridine (104 mg, 0.339 mmol) in anhydrous dichloromethane (4 mL) and stir the solution overnight. Concentrate *in vacuo* and partition the residue between saturated aqueous $NaHCO_3$ and dichloromethane. Extract the aqueous phase with dichloromethane (2 x 15 mL) and EtOAc (2 x 15 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as an oil (62 mg, 88%) that was used without any further purification. MS (ES+) *m/z*: 207 $(M+H)^+$.

Preparation 273

4-Aminomethyl-*N*-cycloheptyl-2-fluoro-benzamide



Methyl 4-bromo-2-fluoro-benzoate: Dissolve 4-bromo-2-fluoro-benzoic acid (15 g, 68.5 mmol) in methanol (70 mL). Add concentrated sulfuric acid (500 µl) to the solution and heat the mixture to reflux for 20 h under a nitrogen atmosphere. Cool the mixture to room temperature and concentrate *in vacuo*. Dissolve the residue in EtOAc (200 mL) and wash successively with saturated aqueous $NaHCO_3$ (50 mL) and water (2 x 50 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (15.4 g, 96%). GC-MS *m/z*: 232 (M^+).

Methyl 4-cyano-2-fluoro-benzoate: Slurry methyl 4-bromo-2-fluoro-benzoate (5 g, 21.5 mmol) and copper(I) cyanide (3.8 g, 42.9 mmol) in anhydrous DMF (90 mL). Heat the mixture to reflux for 20 h under a nitrogen atmosphere. Cool the mixture to room temperature, dilute with hexane/EtOAc (1:1, 300 mL) and water (150 mL). Filter the mixture through Celite® washing with hexane/EtOAc (1:1) to reduce the emulsion layer.

Separate the organic layer and extract the aqueous layer with hexane/EtOAc (1:1, 2 x 200 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1 gradient) to obtain the desired intermediate (2.9 g, 76%). GC-MS *m/z*: 179 (M^+).

4-Cyano-2-fluoro-benzoic acid: Dissolve methyl 4-cyano-2-fluoro-benzoate (2.9 g, 16.2 mmol) in absolute ethanol (100 mL). Add potassium hydroxide (4.5 g, 80.2 mmol) and stir the milky white mixture for 1.5 h. Dilute the mixture with water (125 mL) and wash with diethyl ether (50 mL). Collect the aqueous layer and concentrate *in vacuo* until solids start to appear in the flask, then adjust the mixture to pH 1 with concentrated HCl. Extract the aqueous mixture with diethyl ether (3 x 500 mL). Combine the organic extracts and concentrate *in vacuo* to obtain the desired intermediate as a white solid (2.2 g, 83%).

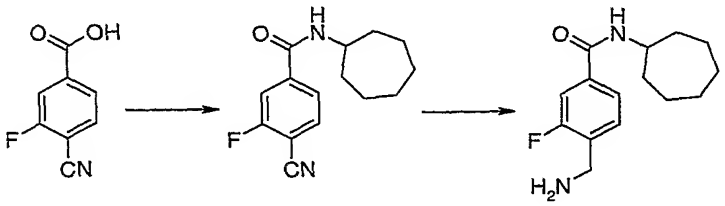
4-Cyano-*N*-cycloheptyl-2-fluoro-benzamide: Dissolve 4-cyano-2-fluoro-benzoic acid (1 g, 6.1 mmol) in anhydrous toluene (25 mL) and thionyl chloride (15 mL). Stir the mixture for 1 h at 90 °C under a nitrogen atmosphere (quench aliquots with methanol and assay by HPLC to determine if starting material has been consumed). Cool the reaction to room temperature and concentrate *in vacuo* to obtain the acid chloride as a yellow oil (1.25 g). Dissolve the acid chloride (1.25 g) in diethyl ether (75 mL), add triethylamine (0.85 mL, 6.1 mmol) and cylcoheptylamine (0.78 mL, 6.1 mmol). Stir the mixture at room temperature for 16 h under a nitrogen atmosphere. Quench the reaction with saturated aqueous Na_2CO_3 (20 mL). Extract the mixture with EtOAc (30 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (1.45 g, 91%). GC-MS *m/z*: 260 (M^+).

4-Aminomethyl-*N*-cycloheptyl-2-fluoro-benzamide: Add 4-cyano-*N*-cycloheptyl-2-fluoro-benzamide (1.4 g, 5.4 mmol), 10% Pd/C (Degussa type E101, 415 mg), ethanol (40 mL), water (15 mL) and acetic acid (1.8 mL) to a pressure vessel. Pressurize the vessel to 55 psi with hydrogen, and stir the mixture for 0.5 h (monitor the reaction by TLC). Filter the mixture through Celite® and wash the cake with warm ethanol followed

by dichloromethane under a nitrogen atmosphere. Concentrate the filtrate *in vacuo* to obtain the product as the acetic acid salt. Use SCX chromatography to obtain the title compound (1.36 g, 95%). GC-MS *m/z*: 264 (M^+).

Preparation 274

4-Aminomethyl-*N*-cycloheptyl-3-fluoro-benzamide

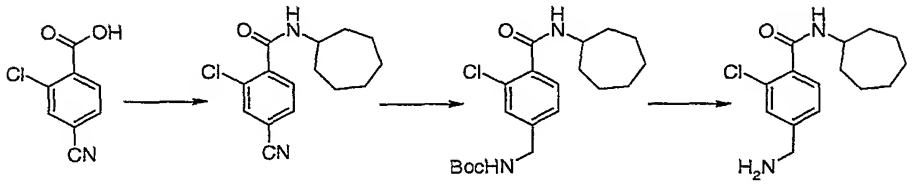


4-Cyano-*N*-cycloheptyl-3-fluoro-benzamide: Dissolve 4-cyano-3-fluoro-benzoic acid (1 g, 6.1 mmol) in anhydrous toluene (20 mL) and thionyl chloride (10 mL). Stir the mixture for 1.5 h at 90 °C under a nitrogen atmosphere (quench aliquots with methanol and assay by HPLC to determine if starting material has been consumed). Cool the reaction to room temperature and concentrate *in vacuo* to obtain the acid chloride as a yellow oil. Dissolve the yellow oil in diethyl ether (50 mL), add triethylamine (0.86 mL, 6.1 mmol) and cycloheptylamine (0.79 mL, 6.1 mmol). Stir the mixture at room temperature for 16 h under a nitrogen atmosphere. Quench the reaction with saturated aqueous Na_2CO_3 (20 mL). Extract the mixture with EtOAc (2 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (1.24 g, 77%). MS (ES-) *m/z*: 259.2 $(M-H)^+$.

4-Aminomethyl-*N*-cycloheptyl-3-fluoro-benzamide: Add 4-cyano-*N*-cycloheptyl-3-fluoro-benzamide (0.86 g, 3.3 mmol), 10% Pd/C (Degussa type E101, 250 mg), ethanol (25 mL), water (9 mL) and acetic acid (1 mL) to a pressure vessel under a nitrogen atmosphere. Pressurize the vessel to 50 psi with hydrogen, and stir the mixture for 0.5 h. Filter the mixture through Celite® and wash the cake with warm ethanol followed by dichloromethane under a nitrogen atmosphere. Concentrate the filtrate *in vacuo* to obtain the title compound as the acetic acid salt. Use SCX chromatography to obtain the title compound (805 mg, 92%). MS (ES+) *m/z*: 265.3 $(M+H)^+$.

Preparation 275

4-Aminomethyl-2-chloro-*N*-cycloheptyl-benzamide



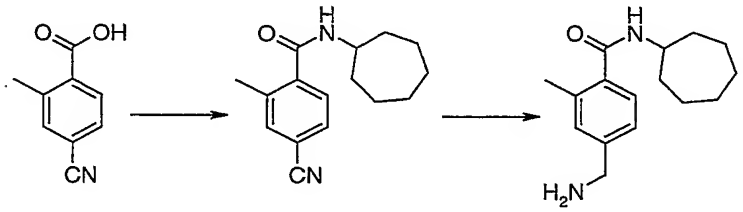
2-Chloro-4-cyano-*N*-cycloheptyl-benzamide: Dissolve 2-chloro-4-cyano-benzoic acid (1.1 g, 6 mmol) in anhydrous toluene (20 mL) and thionyl chloride (15 mL). Stir the mixture for 1 h at 90 °C under a nitrogen atmosphere (quench aliquots with methanol and assay by HPLC to determine if starting material has been consumed). Cool the reaction to room temperature and concentrate *in vacuo* to obtain the acid chloride as an oil. Dissolve the oil in diethyl ether (40 mL), add triethylamine (0.84 mL, 6 mmol) and cycloheptylamine (0.77 mL, 6 mmol). Stir the mixture at room temperature for 1 h under a nitrogen atmosphere. Quench the reaction with saturated aqueous Na_2CO_3 (20 mL). Extract the mixture with EtOAc (100 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with dichloromethane to obtain the desired intermediate (1.1 g, 66%). MS (ES+) *m/z*: 277.2 $(M+H)^+$.

4- *tert*-Butoxycarbonylaminomethyl-2-chloro-*N*-cycloheptyl-benzamide: Dissolve 2-chloro-4-cyano-*N*-cycloheptyl-benzamide (460 mg, 1.7 mmol) in methanol (15 mL). Cool the solution to 0 °C under a nitrogen atmosphere and add di-*tert*-butyl dicarbonate (726 mg, 3.3 mmol) and nickel(II) chloride hexahydrate (40 mg, 0.17 mmol). Add then sodium borohydride (360 mg, 9.5 mmol) portionwise over 30 min. Stir at 0 °C for 1 h then concentrate the mixture *in vacuo*. Dilute the residue with EtOAc (100 mL), wash with saturated aqueous $NaHCO_3$ (40 mL). Extract the aqueous layer with EtOAc (3 x 40 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with EtOAc to obtain the desired intermediate (627 mg, 99%). MS (ES+) *m/z*: 381.3 $(M+H)^+$.

4-Aminomethyl-2-chloro-*N*-cycloheptyl-benzamide: Dissolve 4- *tert*-butoxycarbonylaminomethyl-2-chloro-*N*-cycloheptyl-benzamide (624 mg, 1.6 mmol) in dichloromethane (30 mL) then add trifluoroacetic acid (2 mL). Stir the solution at room temperature under a nitrogen atmosphere for 1 h. Concentrate the mixture *in vacuo*. Purify the crude mixture by SCX chromatography to obtain the desired intermediate (395 mg, 85%). MS (ES+) *m/z*: 281.2 $(M+H)^+$.

Preparation 276

4-Aminomethyl-*N*-cycloheptyl-2-methyl-benzamide



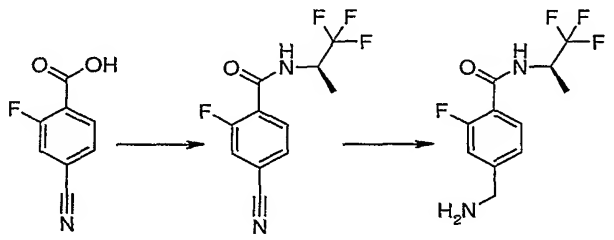
4-Cyano-*N*-cycloheptyl-2-methyl-benzamide: Add cycloheptylamine (0.83 mL, 6.5 mmol), HOBT (838 mg, 6.2 mmol), EDC (1.2 g, 6.2 mmol) and diisopropylethylamine (3.2 mL, 18.6 mmol) to a solution of 4-cyano-2-methyl-benzoic acid (1 g, 6.2 mmol) in dichloromethane (20 mL) at room temperature under a nitrogen atmosphere. Stir the mixture for 16 h at room temperature. Wash the mixture with water (20 mL), separate and concentrate the organic layer *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:2 gradient) to obtain the desired intermediate (830 mg, 52%). MS (ES+) *m/z*: 257.3 $(M+H)^+$.

4-Aminomethyl-*N*-cycloheptyl-2-methyl-benzamide: Add 4-cyano-*N*-cycloheptyl-2-methyl-benzamide (0.82 g, 3.2 mmol), ethanol (23 mL), water (8 mL) and acetic acid (1 mL) to a pressure vessel. Heat vessel to 50 °C to dissolve all solids. Add 10% Pd/C (Degussa type E101, 250 mg) under a nitrogen atmosphere, then pressurize the vessel to 55 psi with hydrogen at ambient temperature. Stir the mixture for 40 min. Filter the mixture through Celite® and wash the cake with warm ethanol (50 mL) followed by dichloromethane (100 mL) under a nitrogen atmosphere. Concentrate the filtrate *in vacuo*

to obtain the title compound as the acetic acid salt. Use SCX chromatography to obtain the title compound (820 mg, 98%). MS (ES+) *m/z*: 261.3 $(M+H)^+$.

Preparation 277

(*R*)-4-Aminomethyl-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide

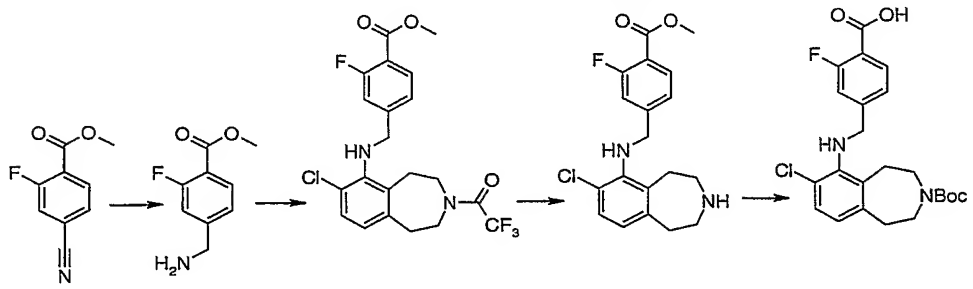


(*R*)-4-Cyano-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide: Add (*R*)-(2,2,2-trifluoro-1-methyl)-ethylamine (0.909 g, 6.08 mmol), HOBT (0.82 g, 6.1 mmol), diisopropylethylamine (2.1 mL, 12 mmol) and EDC (1.17 g, 6.08 mmol) to a mixture of 4-cyano-2-fluorobenzoic acid (1.004 g, 6.08 mmol) in anhydrous THF (40 mL) at room temperature. Stir overnight and partition the mixture between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (100 mL). Dry the organic extract over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with dichloromethane/hexane (1:1 to 1:0 gradient over 71 min; 50 mL/min) to afford the desired intermediate as a white solid (0.985 g, 62%).

(*R*)-4-Aminomethyl-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide: Combine a solution of (*R*)-4-cyano-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide (0.904 g, 3.475 mmol) in absolute ethanol (26 mL), water (9.7 mL) and glacial acetic acid (1.2 mL) with 10% Pd/C (Degussa type E101, 0.27 g, 0.13 mmol) under nitrogen. Purge the mixture with nitrogen and then with hydrogen. Stir the slurry at room temperature under hydrogen at 55 psi for 30 min. Purge the reaction mixture with nitrogen and then filter the slurry over Celite®. Wash the filter cake with ethanol (100 mL) and THF (100 mL). Concentrate the filtrate and purify by SCX chromatography eluting with dichloromethane/methanol (1:1) to remove impurities and then with dichloromethane/2M ammonia in methanol (1:1) to elute product. Concentrate to afford the title compound as a colorless oil (0.86 g, 94%).

Preparation 278

3-*tert*-Butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Methyl 4-aminomethyl-2-fluoro-benzoate: Combine a solution of methyl 4-cyano-2-fluoro-benzoate (1 g, 5.58 mmol) in absolute ethanol (42 mL) and acetic acid (1.9 mL) with a mixture of 10% Pd/C (Degussa type E101, 0.17 g, 0.078 mmol) in water (15.6 mL) at room temperature under nitrogen. Purge with nitrogen and then with hydrogen at 55 psi and stir for 1 h. Purge the reaction with nitrogen, filter through Celite® and wash the filter cake with ethanol (100 mL), THF (100 mL) and isopropanol (100 mL). Concentrate *in vacuo* and purify by SCX chromatography and then chromatography on silica gel (40 g RediSep® column) eluting with dichloromethane/2M ammonia in methanol (99:1 to 9:1 gradient over 30 min; 35 mL/min) to afford the desired intermediate as a white solid (0.602 g, 59%).

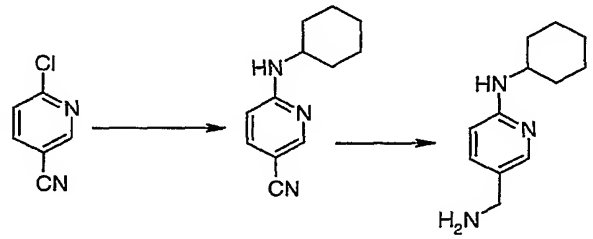
7-Chloro-6-(3-fluoro-4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.24 g, 2.91 mmol) with methyl 4-aminomethyl-2-fluoro-benzoate (1.065 g, 5.821 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (0.533 g, 0.582 mmol), BINAP (0.725 g, 1.16 mmol) and cesium carbonate (3.32 g, 10.2 mmol) under nitrogen in anhydrous toluene (20 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 1:1 gradient over 71 min; 50 mL/min) to afford the desired intermediate as a yellow oil (1.3 g, 100%).

7-Chloro-6-(3-fluoro-4-methoxycarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add 1M aqueous NaOH (2.8 mL, 2.8 mmol) to a solution of 7-chloro-6-(3-fluoro-4-methoxycarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.31 g, 2.86 mmol) in 1,4-dioxane (13.3 mL) and water (2.6 mL) at 11 °C. Allow mixture to warm to room temperature and stir for 1 h. Concentrate *in vacuo* and partition the residue between dichloromethane (250 mL) and saturated aqueous $NaHCO_3$ (100 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to afford the desired intermediate that was used without further purification.

3-*tert*-Butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add 1M aqueous NaOH (5.7 mL, 5.7 mmol) to a mixture of 7-chloro-6-(3-fluoro-4-methoxycarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.04 g, 2.86 mmol) in 1,4-dioxane (13.3 mL) and water (2.6 mL) at room temperature. Heat the mixture at 50 °C for 2 h. Cool the mixture to 0 °C, add a solution of di-*tert*-butyl-dicarbonate (0.62 g, 2.9 mmol) in 1,4-dioxane (2 mL) and stir at 0 °C for 2 h. Concentrate *in vacuo*, add EtOAc (50 mL), 1N aqueous $KHSO_4$ (5.7 mL, 5.7 mmol) and water (20 mL) to pH=1. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to afford the title compound as a yellow oil (1.25 g, 98%) that was used without further purification. MS (ES+) *m/z*: 449.1 $(M+H)^+$.

Preparation 279

5-Aminomethyl-2-cyclohexylamino-pyridine



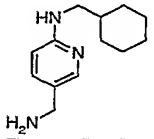
6-Cyclohexylamino-nicotinonitrile: Add cyclohexylamine (7.1 g, 72 mmol) to a mixture of 6-chloronicotinitrile (1 g, 7.2 mmol), potassium carbonate (3 g, 21.7 mmol) and anhydrous DMF (10 mL). Heat the mixture in a sealed flask at 120 °C for 1.5 h.

Cool the reaction to ambient temperature, dilute with hexane/EtOAc (1:1, 100 mL) and wash the mixture with aqueous 5% sodium chloride (3 x 30 mL). Collect the organic layer and concentrate *in vacuo* to obtain the desired intermediate (1.4 g, 97%). GC-MS *m/z*: 201 (M^+).

5-Aminomethyl-2-cyclohexylamino-pyridine: Charge a solution of 6-cyclohexylamino-nicotinonitrile (1.4 g, 7.1 mmol) in methanol (70 mL) and trifluoroacetic acid (5 mL) to a pressure vessel containing 10% Pd/C (Degussa type E101, 600 mg). Pressurize the vessel to 40 psi with hydrogen and stir for 2 h. Filter the mixture through Celite®, wash with warm ethanol, and dichloromethane. Concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to obtain the title compound (920 mg, 54%). MS (ES+) *m/z*: 206.1 $(M+H)^+$.

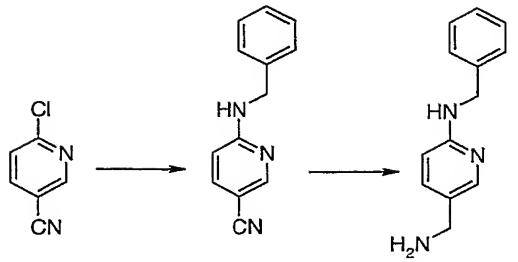
Preparation 280

The compound of Preparation 280 may be prepared essentially as described in Preparation 279 using 6-chloronicotinonitrile and cylclohexylmethylamine. Overall yield and MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
280		5-Aminomethyl-2-cyclohexylmethylamino-pyridine	95	220.3 $(M+H)^+$

Preparation 281

6-Benzylamino-pyridin-3-ylmethylamine

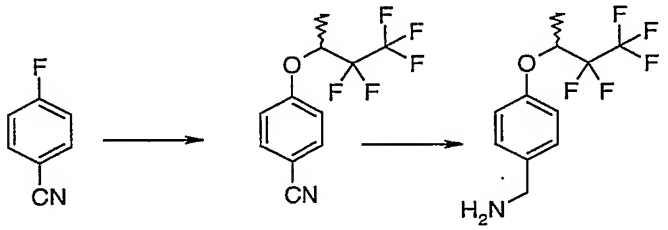


6-Benzylamino-nicotinonitrile: Heat 6-chloroniconitrile (0.58 g, 4.2 mmol) and benzylamine (4.6 mL, 42 mmol) in anhydrous DMF (3 mL) at 120 °C for 4.5 h. Cool at room temperature. Dilute with water and extract with EtOAc. Wash the organic phase with brine, dry over $MgSO_4$, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with hexane/EtOAc (4:1, 2:1, 1:2) to give the desired intermediate as a white solid (840 mg, 96%). MS (ES+) *m/z*: 210 $(M+H)^+$.

6-Benzylamino-pyridin-3-ylmethylamine: Stir 6-benzylamino-nicotinonitrile (680 mg, 3.3 mmol) and 10% Pd/C (Degussa type E101) vigorously in absolute ethanol (80 mL) under hydrogen at 25 psi for 1 h. Filter the solution through Celite® and concentrate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with 2M ammonia in methanol/dichloromethane (4:96, 9:91) to give the title compound as a white solid (320 mg, 45%). MS (ES+) *m/z*: 214 $(M+H)^+$.

Preparation 282

(±)-4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine



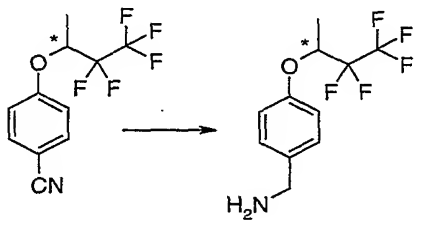
(±)-4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzonitrile: Add potassium carbonate (27.4 g, 198 mmol) to a mixture of 4-fluorobenzonitrile (8 g, 66 mmol) and (±)-3,3,4,4,4-pentafluoro-2-butanol (17.2 g, 105 mmol) in anhydrous DMF (60 mL). Heat the mixture in a sealed flask for 4 h at 130 °C. Cool the reaction to ambient temperature, dilute with

hexane/EtOAc (1:1, 350 mL) and wash with aqueous 5% sodium chloride (3 x 100 mL). Collect the organic layer, dry over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (17.1 g, 98%). GC-MS *m/z*: 432 (M^+).

(±)-4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine: Add (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile (1 g, 3.8 mmol) to a slurry of lithium aluminum hydride (400 mg, 10 mmol) in diethyl ether (30 mL) at 0 °C under a nitrogen atmosphere. Stir the mixture at ambient temperature for 2 h, and then quench the reaction sequentially with water (1 mL) and 5N sodium hydroxide (1 mL). Filter the slurry through Celite®, dry the filtrate over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound (990 mg, 98%). GC-MS *m/z*: 268 (M^+).

Preparation 283

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine Isomer



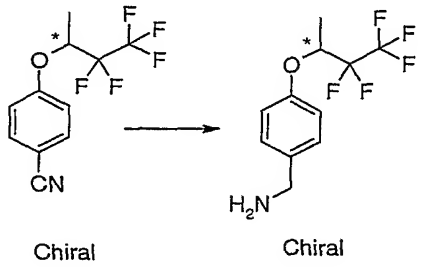
2 Chiral Chiral

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzonitrile Isomer 2: Separate (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile by normal phase chiral chromatography (Chiralcel OJ, 8 x 33 cm, elute with heptane/3A ethanol 97:3, flow rate 375 mL/min). Collect the 2nd eluting isomer as the desired intermediate (11.3 g, 40% recovery, 98.6% ee (Chiralcel OJ, 4.6 x 250 mm, elute with heptane/3A ethanol 97:3, 1 mL/min). GC-MS *m/z*: 265 (M^+).

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine Isomer 2: Reduce 4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile isomer 2 (11.4 g, 43 mmol) using General Procedure 6-4 to obtain the title compound (11.38 g, 98%). GC-MS *m/z*: 268 (M^+).

Preparation 284

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine Isomer 1

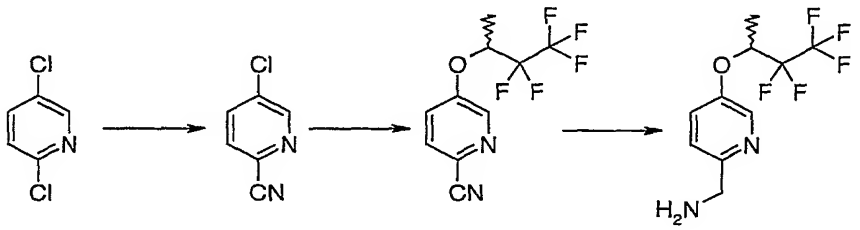


4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzonitrile Isomer 1: Separate (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile by normal phase chiral chromatography (Chiralcel OJ, 8 x 33 cm, elute with heptane/3A ethanol 97:3, flow rate 375 mL/min). Collect the 1st eluting isomer as the desired intermediate (4.5 g, 33% recovery, 99.3% ee (Chiralcel OJ, 4.6 x 250 mm, elute with heptane/3A ethanol 97:3, 1 mL/min). GC-MS *m/z*: 265 (M^+).

4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-benzylamine Isomer 1: Reduce 4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzonitrile isomer 1 (4.5 g, 17 mmol) using General Procedure 6-4 to obtain the title compound (4.3 g, 94%). GC-MS *m/z*: 268 (M^+).

Preparation 285

(±)-2-Aminomethyl-5-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridine



5-Chloro-pyridine-2-carbonitrile: Slurry 2,5-dichloropyridine (6 g, 40.5 mmol), zinc cyanide (2.9 g, 24.7 mmol), zinc (dust) (116 mg, 1.8 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (720 mg, 0.98 mmol) in anhydrous DMF (40 mL). Heat the mixture to reflux under a nitrogen atmosphere for 4.5 h. Cool the mixture to room temperature, dilute with EtOAc

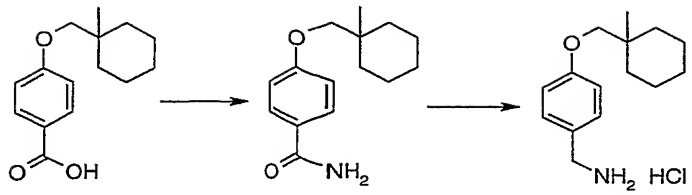
(300 mL), wash with aqueous 10% sodium chloride (3 x 75 mL). Collect organic layer, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1 gradient) to obtain the desired intermediate (2.6 g, 46%). GC-MS *m/z*: 138 (M^+).

(±)-4-[1-(1,1,2,2,2-Pentafluoroethyl)-ethoxy]-pyridine-2-carbonitrile: Add (±)-3,3,4,4,4-pentafluoro-2-butanol (710 mg, 4.3 mmol) slowly to a slurry of sodium hydride (104 mg, 1.2 equiv, 60% mineral oil, washed with hexane) in hexamethylphosphoramide (2 mL) under nitrogen at 0 °C. Allow the slurry to warm to ambient temperature and stir for 5 min. Add 5-chloro-pyridine-2-carbonitrile (300 mg, 2.2 mmol), then heat the mixture in a sealed flask at 130 °C for 4 h (monitor reaction by GC/MS). Cool the reaction to room temperature, adjust the mixture to pH 9 with saturated aqueous Na_2CO_3, then extract with diethyl ether (2 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 7:3 gradient) to obtain the desired intermediate (380 mg, 66%). GC-MS *m/z*: 266 (M^+).

(±)-2-Aminomethyl-5-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridine: Add (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridine-2-carbonitrile (280 mg, 1 mmol), 10% Pd/C (Degussa type E101, 100 mg), methanol (20 mL) and trifluoroacetic acid (3 mL) to a pressure vessel. Pressurize the vessel to 40 psi with hydrogen, and stir the mixture for 1 h (monitor the reaction by TLC). Filter the mixture through Celite® and wash the cake with warm ethanol followed by dichloromethane under a nitrogen atmosphere. Concentrate the filtrate *in vacuo* to obtain the crude product as a trifluoroacetic acid salt. Prepare the free base using SCX chromatography, then purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (20:1) to obtain the title compound (172 mg, 61%). GC-MS *m/z*: 270 (M^+).

Preparation 286

4-(1-Methyl-cyclohexylmethoxy)-benzylamine hydrochloride

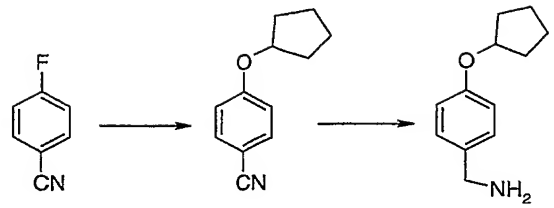


4-(1-Methyl-cyclohexylmethoxy)-benzamide: Add a drop of anhydrous DMF to a mixture of 4-(1-methyl-cyclohexylmethoxy)-benzoic acid (prepared by following the procedure described in *Chem. Pharm. Bull.* **1982**, *30*, 3601-3616) (1 g, 4.03 mmol) and thionyl chloride (3.5 mL) at room temperature. Stir the mixture for 1.5 h and then remove the excess of thionyl chloride *in vacuo*. Take-up the crude acid chloride in anhydrous THF (10 mL) and add the resulting solution to cold concentrated NH_4OH (50 mL). Stir for 2.5 h at room temperature and concentrate *in vacuo*. Collect the solid formed *via* filtration and dry *in vacuo* to obtain the desired intermediate (0.94 g, 94%). MS (ES+) *m/z*: 248 $(M+H)^+$.

4-(1-Methyl-cyclohexylmethoxy)-benzylamine hydrochloride: Add a solution of 4-(1-methyl-cyclohexylmethoxy)-benzamide (6.82 g, 27.6 mmol) in anhydrous THF (75 mL) dropwise over 45 min to a slurry of lithium aluminium hydride (1.57 g, 41.3 mmol) in diethyl ether (100 mL) at room temperature. After the addition is completed, heat the mixture at reflux for 5.5 h. Cool the reaction mixture with an ice bath and quench sequentially with water (1.6 mL), 5N aqueous NaOH (1.6 mL) and water (4.8 mL). Stir the resulting suspension for 1 h and remove the solids formed *via* filtration through Celite® eluting with THF. Dry the filtrate over Na_2SO_4 and treat the solution with an excess of hydrogen chloride in diethyl ether. Concentrate the mixture *in vacuo* to obtain the title compound (6.68 g, 90%). MS (ES+) *m/z*: 233 $(M+H)^+$.

Preparation 287

4-Cyclopentyloxy-benzylamine

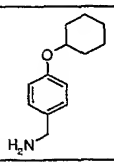
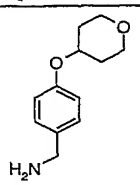
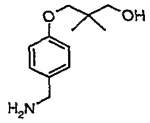
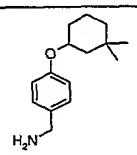
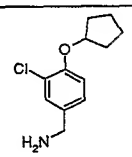


4-Cyclopentyloxy-benzonitrile: Suspend sodium hydride (336 mg, 2.8 mmol, 60% suspension in mineral oil) in anhydrous 1,4-dioxane (10 mL) under nitrogen atmosphere. Add cyclopentanol (620 mg, 7.2 mmol) and stir the resulting solution for 30 min. Add the preformed solution (3.35 mL, 2.4 mmol) to neat 4-fluorobenzonitrile (240 mg, 2 mmol) in a microwave tube and heat the sealed mixture at 100 °C for 30 min. Cool to room temperature and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with isohexane/EtOAc (95:5 to 1:1 gradient) to obtain the desired intermediate (300 mg, 80%). GC-MS *m/z*: 187 (M^+).

4-Cyclopentyloxy-benzylamine: Add a solution of 1M BH_3-THF complex in THF (4.8 mL, 4.8 mmol) to neat 4-cyclopentyloxy-benzonitrile (300 mg, 1.6 mmol) and stir the mixture for 3 h at room temperature and then for 3 h at reflux. Cool to room temperature, pour the reaction into 2N aqueous HCl (10 mL) and stir the mixture for 1 h at room temperature then concentrate *in vacuo*. Dissolve the crude mixture in methanol and filter through SCX column eluting with methanol followed by 3M ammonia in methanol to obtain the title compound (223 mg, 73%).

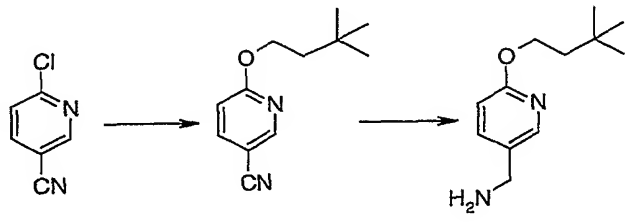
Preparations 288-292

The compounds of Preparations 288-292 may be prepared essentially as described in Preparation 287 using the appropriate alcohols. For Preparations 288, 290 and 291, sodium bis(trimethylsilyl)amide (1.2 equiv., 2M solution in THF) was used as base in the first step. Overall yields and MS (EI) data are shown in the Table below.

Prep.	Structure	Compound	Yield (%)	MS (EI) *m/z*
288		4-Cyclohexyloxy-benzylamine	52	205 (M^+)
289		4-(Tetrahydro-pyran-4-yloxy)-benzylamine	42	207 (M^+)
290		3-(4-Aminomethyl-phenoxy)-2,2-dimethyl-propan-1-ol	38	209 (M^+)
291		(±)-4-(3,3-Dimethyl-cyclohexyloxy)-benzylamine	37	233 (M^+)
292		3-Chloro-4-cyclopentyloxy-benzylamine	42	225 (M^+)

Preparation 293

5-Aminomethyl-2-(3,3-dimethyl-butoxy)-pyridine



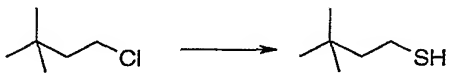
6-(3,3-Dimethyl-butoxy)-nicotinonitrile: Add sodium bis(trimethylsilyl)amide (3.95 mL, 7.9 mmol, 2M solution in THF) to a solution of 3,3-dimethyl-butan-1-ol (960 □L, 7.9 mmol) in anhydrous THF (10 mL). Stir for 30 min at room temperature and then add a solution of 6-chloro-nicotinonitrile (1 g, 7.2 mmol) in anhydrous THF (5 mL). Stir at room temperature overnight and then quench the reaction mixture with saturated aqueous

$NaHCO_3$ (100 mL). Extract the aqueous layer with dichloromethane (3 x 100 mL) and wash the organic layer with brine (100 mL). Dry the combined organic extracts over $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as a yellow solid (1.4 g, 94%). GC-MS *m/z*: 204 (M^+).

5-Aminomethyl-2-(3,3-dimethyl-butoxy)-pyridine: Dissolve 6-(3,3-dimethyl-butoxy)-nicotinonitrile (1.4 g, 6.86 mmol) in anhydrous THF (10 mL) under nitrogen and add 1M BH_3-THF complex in THF (20.6 mL, 20.6 mmol). Stir the mixture overnight under nitrogen and then pour the reaction carefully into 5N aqueous HCl (20 mL). Stir the resulting suspension for 6 h at room temperature. Then basify by adding 2N aqueous NaOH (50 mL) and extract with dichloromethane (3 x 100 mL). Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo*. Take-up the resulting oil in methanol and filter it through an SCX column eluting with methanol followed by 3M ammonia in methanol. Concentrate *in vacuo* to obtain the title compound (754 g, 50%). GC-MS *m/z*: 208 (M^+).

Preparation 294

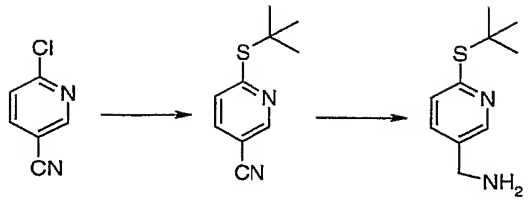
3,3-Dimethylbutanethiol



Into four separate microwave tubes add thiourea (630 mg, 8.3 mmol) to a solution of 1-chloro-3,3-dimethylbutane (0.5 g, 4.4 mmol) in ethanol (5 mL) and heat in a sealed tube in a microwave reactor at 150 W at 100 °C for 4 h. Cool to room temperature then stand over three days. Combine the reactions and concentrate *in vacuo* to afford a white solid. Add 2M aqueous NaOH (50 mL) and heat at reflux overnight. Cool to room temperature then acidify to pH 2 with 5M aqueous HCl (20 mL). Extract into diethyl ether (50 mL), wash with brine (30 mL) then dry over $MgSO_4$ and concentrate *in vacuo* to give the title compound as a clear oil (2 g, 100%).

Preparation 295

5-Aminomethyl-2-*tert*-butylthio-pyridine



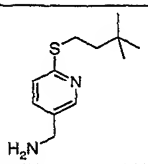
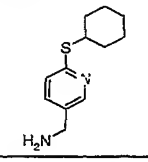
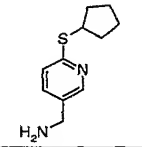
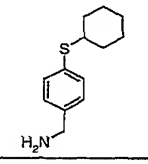
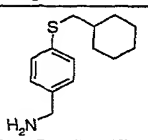
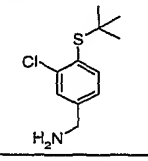
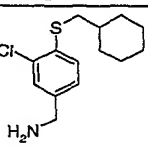
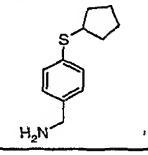
6-(*tert*-Butylthio)nicotinonitrile: Add sodium ethoxide (12 mL of 21% w/v in ethanol, 36 mmol) to a solution of 2-methyl-2-propanethiol (4.06 mL, 36 mmol) in anhydrous ethanol (90 mL) at 0 °C under nitrogen atmosphere. Stir the solution and allow it to warm to room temperature over 30 min. Add 6-chloronicotinonitrile (5 g, 36 mmol) and then heat the reaction to reflux overnight. Cool to room temperature, add saturated aqueous $NaHCO_3$ and concentrate *in vacuo*. Extract into EtOAc or dichloromethane and wash with brine. Dry over $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as orange crystals (6.31 g, 91%). MS (ES+) *m/z*: 193 $(M+H)^+$.

5-Aminomethyl-2-*tert*-butylthio-pyridine: Use a method similar to the General Procedure 6-5 to react 6-(*tert*-butylthio)nicotinonitrile (4.4 g, 22.7 mmol) in anhydrous THF (25 mL) with 1M BH_3-THF complex in THF (25 mL, 25 mmol). Add 5M aqueous HCl (10 mL) cautiously and stir the mixture overnight at room temperature. Extract into EtOAc, wash with brine, dry over $MgSO_4$ and concentrate *in vacuo* to give an orange solid. Dissolve the crude mixture in methanol and filter through an SCX column eluting with methanol followed by 3M ammonia in methanol to obtain the title compound (2.74 g, 61%). MS (ES+) *m/z*: 197 $(M+H)^+$.

Preparations 296-303

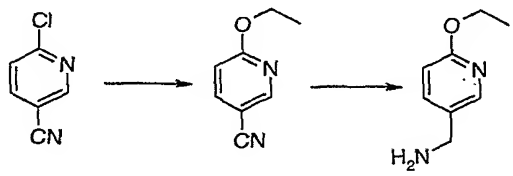
The compounds of Preparations 296-303 may be prepared essentially as described in Preparation 295 using the appropriate thiol and 6-chloronicotinonitrile (Preparations 296-298) or the appropriate aryl fluoride (Preparations 299-303). Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	Yield (%)	MS (ES+) *m/z*

296		5-Aminomethyl-2-(3,3-dimethyl-butylthio)-pyridine	5	225 $(M+H)^+$
297		5-Aminomethyl-2-cyclohexylthio-pyridine	47	223 $(M+H)^+$
298		5-Aminomethyl-2-cyclopentylthio-pyridine	63	209 $(M+H)^+$
299		4-Cyclohexylthio-benzylamine	30	205 $(M+H-NH_3)^+$
300		4-Cyclohexylmethylthio-benzylamine	30	219 $(M+H-NH_3)^+$
301		4-*tert*-Butylthio-3-chloro-benzylamine	52	213 $(M+H-NH_3)^+$
302		4-Cyclohexylmethylthio-3-chloro-benzylamine	31	253 $(M+H-NH_3)^+$
303		4-Cyclopentyllthio-benzylamine	61	208 $(M+H)^+$

Preparation 304

5-Aminomethyl-2-ethoxy-pyridine

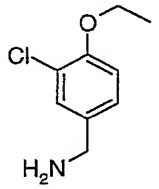


6-(Ethoxy)nicotinonitrile: Add sodium ethoxide (1.6 mL of 21% w/v in ethanol, 4.8 mmol) to a solution of 6-chloronicotinonitrile (612 mg, 4.41 mmol) in anhydrous ethanol (15 mL) and heat the reaction at reflux for 3 h. Cool to room temperature and stir overnight under nitrogen atmosphere. Concentrate *in vacuo* and dissolve the residue into dichloromethane. Wash with saturated aqueous $NaHCO_3$, dry over $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as an off-white solid (545 mg, 83%).

5-Aminomethyl-2-ethoxy-pyridine: Add a solution of 1M BH_3-THF complex in THF (7 mL, 7 mmol) to a solution of 6-(ethoxy)nicotinonitrile (911 mg, 4.41 mmol) in anhydrous THF (7 mL) and stir the mixture overnight at reflux. Add a second aliquot of 1M BH_3-THF complex in THF (7 mL, 7 mmol) and stir the mixture overnight at reflux. Add 5N aqueous HCl (10 mL) cautiously and stir the mixture overnight at room temperature. Concentrate *in vacuo* then dissolve the crude mixture in methanol and filter through an SCX column eluting with methanol followed by 3M ammonia in methanol to obtain the title compound (250 mg, 40%). MS (ES+) *m/z*: 153 $(M+H)^+$.

Preparation 305

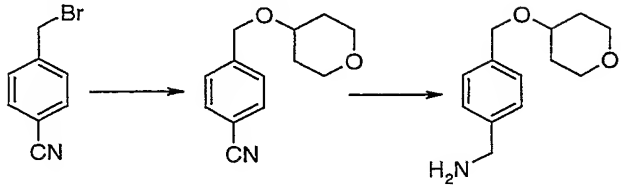
4-Ethoxy-3-chloro-benzylamine



The compound of Preparation 305 may be prepared essentially as described in Preparation 304 using the appropriate aryl fluoride (38% yield, MS (ES+) *m/z* 169 $(M+H-NH_3)^+$).

Preparation 306

4-(Tetrahydro-pyran-4-yloxymethyl)-



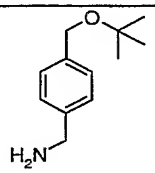
benzylamine

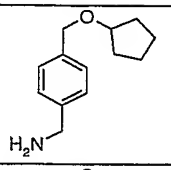
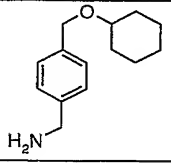
4-(Tetrahydro-pyran-4-yloxymethyl)-benzonitrile: Add sodium bis(trimethylsilyl)amide (2.8 mL, 5.61 mmol, 2M solution in THF) to a solution of tetrahydro-pyran-4-ol (572 mg, 5.61 mmol) in anhydrous THF (20 mL) and stir for 30 min. Add a solution of 4-bromomethyl-benzonitrile (1 g, 5.1 mmol) in anhydrous THF (5 mL) and stir the resulting mixture overnight at room temperature. Concentrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with cyclohexane/EtOAc (98:2 to 1:1 gradient) to obtain the desired intermediate as a white solid (845 mg, 76%). GC-MS *m/z*: 217 (M^+).

4-(Tetrahydro-pyran-4-yloxymethyl)-benzylamine: Use a method similar to the General Procedure 6-5 to reduce 4-(tetrahydro-pyran-4-yloxymethyl)-benzonitrile (845 mg, 4 mmol). Reflux overnight to obtain the title compound (812 mg, 91%). MS (ES+) *m/z*: 222.2 $(M+H)^+$.

Preparations 307-309

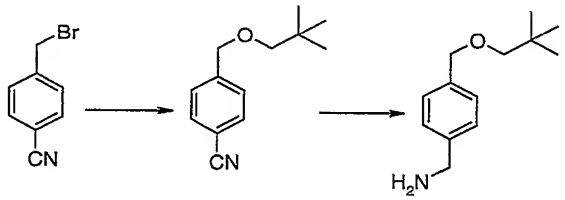
The compounds of Preparations 307-309 may be prepared essentially as described in Preparation 306 using 4-bromomethyl-benzonitrile and the appropriate alcohol. Overall yields and MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
307		4-*tert*-Butoxymethyl-benzylamine	22	194 $(M+H)^+$

308		4-Cyclopentyloxymethyl-benzylamine	72	206 $(M+H)^+$
309		4-Cyclohexyloxymethyl-benzylamine	58	220 $(M+H)^+$

Preparation 310

4-(2,2-Dimethyl-propoxymethyl)-benzylamine

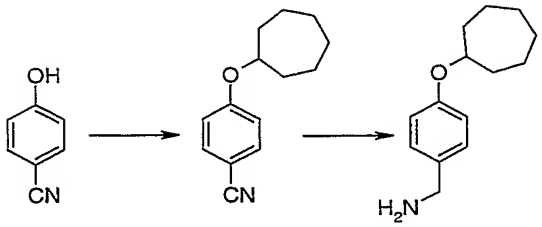


4-(2,2-Dimethyl-propoxymethyl)-benzonitrile: Add sodium bis(trimethylsilyl)amide (3 mL, 6 mmol, 2M solution in THF) to a solution of 2,2-dimethyl-1-propanol (528 mg, 6 mmol) in anhydrous 1,4-dioxane. Stir until the suspension becomes homogenous. Then add a solution of 4-cyanobenzyl bromide (980 mg, 5 mmol) in anhydrous 1,4-dioxane (3 mL). Heat the mixture in a microwave oven at 100 °C for 30 min. Cool to room temperature, add water (50 mL) and extract with EtOAc (3 x 50 mL). Dry the combined organic extracts over $MgSO_4$, and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (95:5 to 1:1 gradient) to obtain the desired intermediate (811 mg, 80%).

4-(2,2-Dimethyl-propoxymethyl)-benzylamine: Add 1M BH_3-THF complex in THF (16 mL, 16 mmol) to neat 4-(2,2-dimethyl-propoxymethyl)-benzonitrile (3.043 g, 15 mmol) and stir the mixture overnight at room temperature. Add methanol and stir until hydrogen evolution stops. Concentrate the solution *in vacuo*. Dissolve the crude mixture in methanol and filter through an SCX column eluting with methanol followed by 3M ammonia in methanol. Concentrate *in vacuo* to obtain the title compound (3 g, 96%).

Preparation 311

4-Cycloheptyloxy-benzylamine

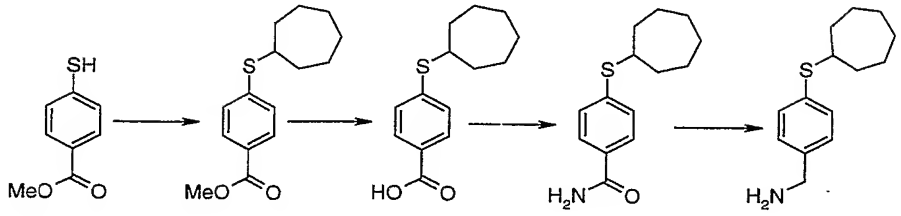


4-Cycloheptyloxy-benzonitrile: Under a nitrogen atmosphere, add 4-hydroxybenzonitrile (4 g, 33.5 mmol), cycloheptanol (2.55 g, 22.3 mmol), tri-*n*-butylphosphine (8.25 mL, 33.5 mmol), and azodicarboxylate dipiperidine (8.45 g, 33.5 mmol) to anhydrous THF (60 mL) at 0 °C. Stir the mixture at 0 °C for 1 h and then at room temperature for 12 h. Dilute with EtOAc (50 mL) and water (50 mL). Separate the layers and extract the aqueous phase with EtOAc (4 × 30 mL). Wash the combined organic extracts with water (30 mL) and brine (20 mL). Dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (120 g RediSep column) eluting with hexane/EtOAc (1:0 to 1:1 gradient over 1.25 h; 80 mL/min) to provide the desired intermediate as a colorless oil (2.77 g, 58%). MS (APCI) *m/z*: 216 $(M+H)^+$.

4-Cycloheptyloxy-benzylamine: Dissolve 4-cycloheptyloxy-benzonitrile (2 g, 9.29 mmol) in anhydrous THF (20 mL) and cool to 0 °C. Add borane dimethylsulfide complex (2.8 mL, 27.9 mmol, 10-12 M solution), stir at 0 °C for 0.5 h and then heat at reflux for 1 h. Cool the mixture to 0 °C, add methanol (5 mL) and stir for 15 min. Add 2M aqueous HCl (15 mL) and stir for 30 min at room temperature. Concentrate the mixture *in vacuo* and purify the residue by chromatography on silica gel (45 g RediSep column) eluting with a gradient of dichloromethane in chloroform/methanol/concentrated ammonium hydroxide (80:18:2) over 30 min (80 mL/min) to provide the title compound as a colorless oil (1.87 g, 97%). MS (APCI) *m/z*: 220 $(M+H)^+$.

Preparation 312

4-Cycloheptylthio-benzylamine



Methyl 4-cycloheptylthio-benzoate: Under a nitrogen atmosphere, add methyl 4-mercaptobenzoate (2.5 g, 15 mmol), cycloheptanol (2.55 g, 22.3 mmol), tri-*n*-butylphosphine (5.26 g, 26 mmol) and azodicarboxylate dipiperidine (6.56 g, 26 mmol) to anhydrous THF (50 mL) at 0 °C. Stir the mixture at 0 °C for 1 h and then at room temperature for 12 h. Dilute with EtOAc (50 mL) and water (50 mL) and extract the aqueous phase with EtOAc (4 × 30 mL). Wash the combined organic extracts with water (30 mL) and brine (20 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (120 g RediSep column) eluting with hexane/EtOAc (1:0 to 1:1 gradient over 1.25 h; 80 mL/min) to provide the desired intermediate as a colorless oil (1.12 g, 40%). MS (APCI) *m/z*: 265 $(M+H)^+$.

4-Cycloheptylthio-benzoic acid: Add methyl 4-cycloheptylthio-benzoate (1.1 g, 4.16 mmol) and sodium hydroxide (500 mg, 12.5 mmol) to methanol (20 mL) and stir overnight. Add 2M aqueous HCl (20 mL) and extract the aqueous phase with dichloromethane. Wash the combined organic extracts with water (20 mL) and brine (20 mL). Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as a white solid (984 mg, 94%). MS (APCI) *m/z*: 251 $(M+H)^+$.

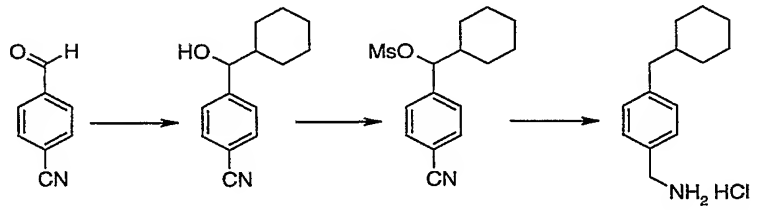
4-Cycloheptylthio-benzamide: Add thionyl chloride (1.35 mL, 18.4 mmol) to a mixture of 4-cycloheptylthio-benzoic acid (984 mg, 3.93 mmol) in dichloromethane (15 mL) at 0 °C. Heat the mixture to reflux for 1 h. Cool the mixture to room temperature and concentrate *in vacuo*. Dissolve the residue in dichloromethane (20 mL) and cool to 0 °C. Add triethylamine (1.1 mL, 7.86 mmol) and bubble ammonia gas through the solution.

Warm the mixture to room temperature and stir for 1 h. Dilute with water (20 mL) and extract the aqueous phase with dichloromethane (3 × 20 mL). Wash the combined organic extracts with saturated aqueous $NaHCO_3$ (20 mL). Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as an off-white solid (976 mg, 99%). MS (APCI) *m/z*: 250 $(M+H)^+$.

4-Cycloheptylthio-benzylamine: Under a nitrogen atmosphere, add 4-cycloheptylthio-benzamide (976 mg, 3.91 mmol) to a slurry of lithium aluminum hydride (0.398 mg, 11.7 mmol) in anhydrous THF (25 mL) at 0 °C. Heat the mixture for 1 h. Cool the mixture to 0 °C and add diethyl ether (50 mL). Carefully add water (0.4 mL), 3M aqueous NaOH (0.4 mL) and water (1.2 mL). Filter the solid residue and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (45 g RediSep column) eluting with a gradient of dichloromethane in chloroform/methanol/concentrated ammonium hydroxide (80:18:2) over 45 min (80 mL/min) to give the title compound as a colorless oil (530 mg, 57%). MS (ES+) *m/z*: 236 $(M+H)^+$.

Preparation 313

4-Cyclohexylmethyl-benzylamine hydrochloride



4-(Cyclohexyl-hydroxy-methyl)-benzonitrile: Dissolve 4-formyl-benzonitrile (5 g, 38.1 mmol) in anhydrous toluene (50 mL). Add chlorodicyclohexylborane (39 mL, 39 mmol, 1M solution in hexane) and 2,6-lutidine (4.25 mL, 39 mmol) and stir the mixture overnight at room temperature. Cool to 0 °C, add aqueous hydrogen peroxide (5.4 mL, 48 mmol, 30%) and 3M aqueous NaOH (16 mL, 48 mmol) and stir for 15 min. Add EtOAc and extract the aqueous phase with EtOAc. Wash the combined organic extracts with water and brine. Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (45 g RediSep column)

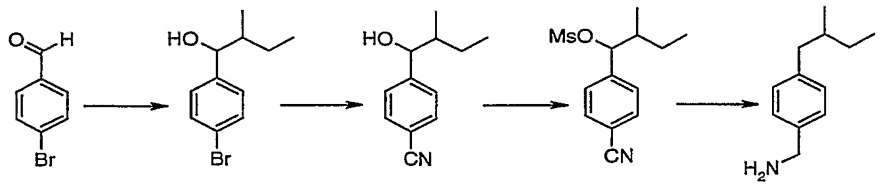
eluting with hexane/EtOAc (1:0 to 1:1 gradient over 60 min; 80 mL/min) to provide the desired intermediate as a clear oil (2.3 g, 23%). MS (APCI) *m/z*: 197 $(M-H_2O)^+$.

4-(Cyclohexyl-methanesulfonyloxy-methyl)-benzonitrile: Dissolve 4-(cyclohexyl-hydroxy-methyl)-benzonitrile (1 g, 4.66 mmol), and triethylamine (1.3 mL, 9.3 mmol) in dichloromethane (20 mL). Cool the mixture to 0 °C, add methanesulfonyl chloride (1.49 mL, 5.34 mmol) and stir the solution for 2 h at 0 °C. Add water (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). Separate the layers and extract back the aqueous phase with dichloromethane (3 × 20 mL). Combine the organic layers, wash with water (20 mL), dry over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as a yellow oil (1.29 g, 94%). MS (APCI) *m/z*: 294 $(M+H)^+$.

4-Cyclohexylmethyl-benzylamine hydrochloride: Dissolve 4-(cyclohexyl-methanesulfonyloxy-methyl)-benzonitrile (1.36 g, 4.64 mmol) in diethyl ether (20 mL) and cool the solution to 0 °C. Add lithium aluminum hydride (528 mg, 13.9 mmol) and stir the mixture at 0 °C for 2 h and then at room temperature for 3 h. Cool the mixture to 0 °C and carefully add water (0.5 mL), 3M aqueous NaOH (0.55 mL), and water (1.5 mL). Filter the solid residue and concentrate the filtrate *in vacuo*. Dissolve the crude mixture in diethyl ether and bubble hydrogen chloride to form a white precipitate. Filter and dry the solid *in vacuo* to provide the title compound as a white solid (420 mg, 44%). MS (APCI) *m/z*: 204 $(M+H)^+$.

Preparation 314

4-(2-Methyl-butyl)-benzylamine



4-(1-Hydroxy-2-methyl-butyl)-1-bromo-benzene: Add slowly a solution of 2-bromo-butane (4.8 g, 35 mmol) in anhydrous THF (20 mL) to a stirring mixture of magnesium

(980 mg, 37 mmol) and anhydrous THF (10 mL) under a nitrogen atmosphere. Heat the mixture at reflux for 30 min. Cool the mixture to room temperature and add 4-bromo-benzaldehyde (5.36 g, 29 mmol). After stirring for 5 min, cool the mixture in an ice-bath and acidify with 3N aqueous HCl (50 mL). Dilute the mixture with water and extract twice with diethyl ether. Wash the combined organic extracts with water and brine. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 20:1 and 1:1) to provide the desired intermediate as a clear oil (2 g, 28%). MS (APCI) *m/z*: 243 $(M+H)^+$.

4-(1-Hydroxy-2-methyl-butyl)-benzonitrile: Add 4-(1-hydroxy-2-methyl-butyl)-1-bromo-benzene (1.9 g, 7.8 mmol), zinc cyanide (1.82 g, 15.6 mmol), and tetrakistriphenylphosphine palladium(0) (260 mg, 0.22 mmol) to anhydrous DMF (40 mL) under a nitrogen atmosphere. Heat the mixture at 90 °C for 12 h. Cool the mixture to room temperature, dilute with water and extract the aqueous phase twice with dichloromethane. Wash the combined organic extracts with water and brine. Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 20:1) to provide the desired intermediate (1.2 g, 75%). MS (APCI) *m/z*: 190 $(M+H)^+$.

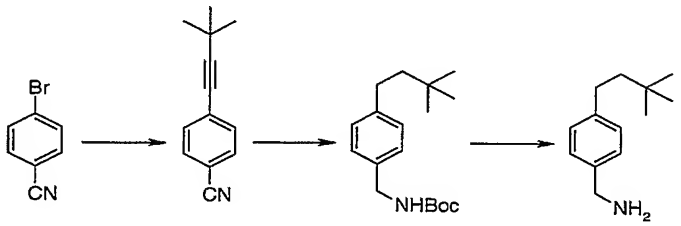
4-(1-Methanesulfonyloxy-2-methyl-butyl)-benzonitrile: Add methanesulfonyl chloride (540 mg, 4.72 mmol) to a solution of 4-(1-hydroxy-2-methyl-butyl)-benzonitrile (800 mg, 4.23 mmol) and triethylamine (0.88 mL, 6.35 mmol) in dichloromethane (10 mL) at 0 °C. Warm the mixture to room temperature and stir for 1 h. Dilute the mixture with water and dichloromethane. Extract the aqueous layer with dichloromethane. Wash the combined organic extracts with water. Dry the organic solution over Na_2SO_4, filter and concentrate *in vacuo* to provide the desired intermediate as a clear oil (1.38 g) that was used without further purification. MS (APCI) *m/z*: 268 $(M+H)^+$.

4-(2-Methyl-butyl)-benzylamine: Under a nitrogen atmosphere, add a mixture of 4-(1-methanesulfonyloxy-2-methyl-butyl)-benzonitrile (1.3 g, 4.9 mmol) in diethyl ether (5 mL) to a slurry of lithium aluminum hydride (820 mg, 19.5 mmol) in diethyl ether (25

mL) at 0 °C. Heat the mixture under reflux for 1 h. Cool the mixture in an ice-bath and add water (0.9 mL), 15% aqueous NaOH (0.9 mL) and water (2.8 mL). Apply the mixture to a silica gel column eluting with dichloromethane and 5:1 dichloromethane in chloroform/methanol/concentrated ammonium hydroxide (80:18:2) to provide the title compound (450 mg, 52%). MS (ES+) *m/z*: 178 $(M+H)^+$.

Preparation 315

4-(3,3-Dimethyl-butyl)-benzylamine



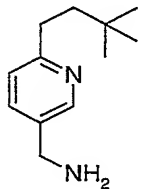
4-(3,3-Dimethyl-but-1-ynyl)-benzonitrile: Dissolve 4-bromobenzonitrile (3 g, 16.48 mmol) in anhydrous DMF (30 mL) in a sealed tube. Degas the solution, purge with nitrogen and add tris(dibenzylideneacetone)dipalladium(0) (453 mg, 0.49 mmol), copper(I) iodide (188 mg, 0.99 mmol), triphenylphosphine (1.08 g, 4.12 mmol), triethylamine (10 mL) and 3,3-dimethylbutyne (6.1 mL, 49.44 mmol). Heat the mixture at 90 °C overnight. Cool to room temperature, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1, 9:1) to give the desired intermediate as a solid (2.75 g, 92%).

***N*-(*tert*-Butoxycarbonyl)-4-(3,3-dimethyl-butyl)-benzylamine:** Dissolve 4-(3,3-dimethyl-but-1-ynyl)-benzonitrile (0.85 g, 4.64 mmol) in methanol (50 mL). Add 10% Pd/C (Degussa type E101, 0.68 g) and di-*tert*-butyl-dicarbonate (1.21 g, 5.57 mmol). Submit the mixture to hydrogenation under atmospheric pressure (balloon) for 6 h. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (9:1, 4:1) to provide the desired intermediate as an oil (1.25 g, 93%). MS (ES+) *m/z*: 314 $(M+Na)^+$.

4-(3,3-Dimethyl-butyl)-benzylamine: Add 4N hydrogen chloride in dioxane (15 mL) to a stirred solution of *N*-(*tert*-butoxycarbonyl)-4-(3,3-dimethyl-butyl)-benzylamine (1.25 g, 4.29 mmol) in methanol (20 mL) and stir at room overnight. Concentrate *in vacuo* and wash the solid with diethyl ether. Suspend the solid in dichloromethane and saturated aqueous $NaHCO_3$ and stir until both phases are clear (15 min). Extract the aqueous phase twice with dichloromethane. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to give the title compound as an oil (0.654 g, 80%) that was used without any further purification. MS (ES+) *m/z*: 192 $(M+H)^+$.

Preparation 316

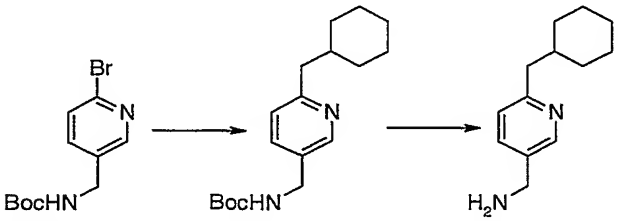
3-Aminomethyl-6-(3,3-dimethyl-butyl)-pyridine



The title compound may be prepared essentially as described in Preparation 315 by using 6-bromonicotinonitrile (45% yield, MS (ES+) *m/z* 193 $(M+H)^+$).

Preparation 317

3-Aminomethyl-6-cyclohexylmethyl-pyridine



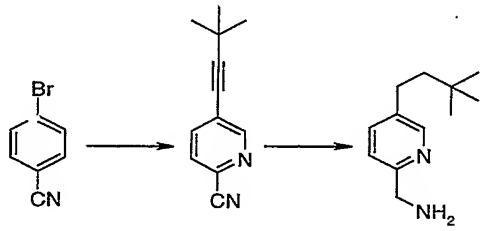
3-*tert*-Butoxycarbonylaminomethyl-6-cyclohexylmethyl-pyridine: Dissolve 2-bromo-5-*tert*-butoxycarbonylaminomethyl-pyridine (500 mg, 1.74 mmol) in anhydrous THF (5 mL) in a sealed tube. Degas the solution, purge with nitrogen and add 1,1′-[bis(diphenylphosphino)ferrocene]dichloropalladium(II) (127 mg, 0.174 mmol) and 0.5M cyclohexylmethylzinc bromide in THF (10.4 mL, 5.22 mmol). Heat the mixture at 60 °C

overnight. Cool to room temperature and dilute the reaction mixture with EtOAc. Add water and filter the precipitate over Celite®. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (4:1, 3:2) to give the desired intermediate as an oil (359 mg, 68%). MS (ES+) *m/z*: 305 $(M+H)^+$.

3-Aminomethyl-6-cyclohexylmethyl-pyridine: Add 4N hydrogen chloride in dioxane (10 mL) to a solution of 3-*tert*-butoxycarbonylaminomethyl-6-cyclohexylmethyl-pyridine (345 mg, 1.13 mmol) in EtOAc (10 mL) and stir overnight. Concentrate *in vacuo*, suspend the solid obtained in diethyl ether and add hexane. Filter and wash the solid with hexane. Suspend the solid into dichloromethane, add saturated aqueous $NaHCO_3$ and stir until both phases are clear (15 min). Extract the aqueous phase twice with dichoromethane. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to obtain the title compound as an oil (205 mg, 97%) that was used without any further purification. MS (ES+) *m/z*: 205 $(M+H)^+$.

Preparation 318

2-Aminomethyl-5-(3,3-dimethyl-butyl)-pyridine



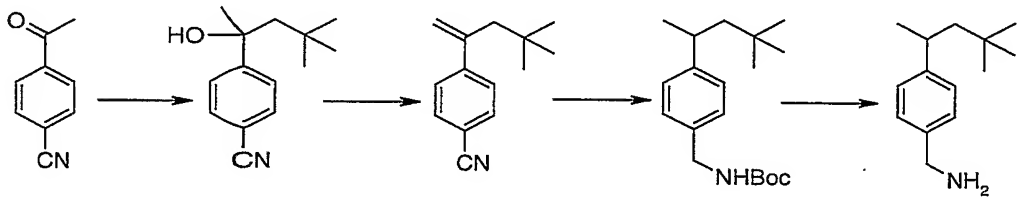
5-(3,3-Dimethyl-but-1-ynyl)-2-cyano-pyridine: Dissolve 5-bromo-2-cyano-pyridine (316 mg, 1.72 mmol) in anhydrous DMF (7 mL) in a sealed tube. Degas the solution, purge with nitrogen and add tris(dibenzylideneacetone)dipalladium(0) (47 mg, 0.05 mmol), copper(I) iodide (20 mg, 0.1 mmol), triphenylphosphine (113 mg, 0.43 mmol), triethylamine (2 mL) and 3,3-dimethylbutyne (0.64 mL, 5.16 mmol). Heat the mixture at 90 °C overnight. Cool to room temperature, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate

in vacuo. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as a solid (310 mg, 97%).

2-Aminomethyl-5-(3,3-dimethyl-butyl)-pyridine: Dissolve 5-(3,3-dimethyl-but-1-ynyl)-2-cyano-pyridine (255 mg, 1.5 mmol) in methanol (15 mL). Add 10% Pd/C (Degussa type E101, 230 mg) and submit the mixture to hydrogenation under atmospheric pressure (balloon) overnight. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo* to provide the title compound as a solid (231 mg, 87%) that was used without any further purification. MS (ES+) *m/z*: 193 $(M+H)^+$.

Preparation 319

4-(1,3,3-Trimethyl-butyl)-benzylamine



4-(1-Hydroxy-1,3,3-trimethyl-butyl)-benzonitrile: Dissolve 4-acetylbenzonitrile (1 g, 6.88 mmol) in diethyl ether/THF (1:1, 60 mL) and cool the solution to 0 °C. Add 1M neopentylmagnesium chloride in diethyl ether (8.3 mL, 8.3 mmol) under nitrogen and stir the mixture at room temperature overnight. Add saturated aqueous NH_4Cl and extract the mixture twice with EtOAc. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1, 9:1) to give the desired intermediate (364 mg, 24%).

4-(3,3-Dimethyl-1-methylene-butyl)-benzonitrile: Add *p*-toluenesulfonic acid monohydrate (308 mg, 1.62 mmol) to a solution of 4-(1-hydroxy-1,3,3-trimethyl-butyl)-benzonitrile (352 mg, 1.62 mmol) in toluene (10 mL). Heat the solution to 100 °C for 30 min. Cool the reaction mixture to room temperature, dilute the reaction mixture with EtOAc and wash the organic phase with saturated aqueous $NaHCO_3$. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by

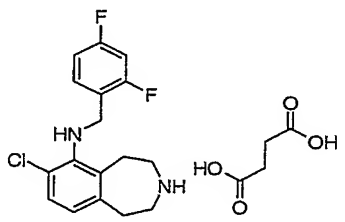
chromatography on silica gel eluting with hexane and hexane/EtOAc (98:2, 19:1) to give the desired intermediate as an oil (200 mg, 62%).

N-(*tert*-Butoxycarbonyl)-4-(1,3,3-trimethyl-butyl)-benzylamine: Dissolve 4-(3,3-dimethyl-1-methylene-butyl)-benzonitrile (164 mg, 0.82 mmol) in methanol (15 mL). Add 10% Pd/C (Degussa type E101, 130 mg) and di-*tert*-butyl-dicarbonate (197 mg, 0.902 mmol). Submit the mixture to hydrogenation under atmospheric pressure (balloon) for 3 h. Filter the catalyst through Celite® and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1, 9:1) to provide the desired intermediate as an oil (227 mg, 90%). MS (ES+) *m/z*: 328 $(M+Na)^+$.

4-(1,3,3-Trimethyl-butyl)-benzylamine: Add 4N hydrogen chloride in dioxane (10 mL) to a stirred solution of *N*-(*tert*-butoxycarbonyl)-4-(1,3,3-trimethyl-butyl)-benzylamine (225 mg, 0.74 mmol) in EtOAc (15 mL) and stir the mixture at ambient temperature overnight. Concentrate *in vacuo* and wash the solid with diethyl ether. Suspend the solid in dichloromethane and saturated aqueous $NaHCO_3$ and stir until both phases are clear (15 min). Extract the aqueous phase twice with dichloromethane. Dry the combined organic extracts over $MgSO_4$, filter and concentrate *in vacuo* to give the title compound as an oil (0.136 g, 90%) that was used without any further purification. MS (ES+) *m/z*: 206 $(M+H)^+$.

Example 537

7-Chloro-6-(2,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



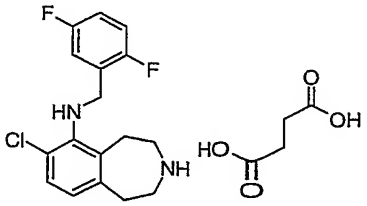
Use a method similar to the General Procedure 5-1 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3

g, 7.06 mmol), palladium(II) acetate (0.16 g, 0.71 mmol), BINAP (0.88 g, 1.41 mmol), 2,4-difluorobenzylamine (3.03 g, 21.18 mmol) and cesium carbonate (3.22 g, 9.88 mmol) in degassed toluene (120 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 16 h. Cool the mixture to room temperature, dilute with EtOAc, filter through Celite® and concentrate *in vacuo* to give a brown oil. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/THF (95:5) to obtain 7-chloro-6-(2,4-difluorobenzylamino)-3-(2,2,2,trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (2.25 g, 76%). MS (ES+) *m/z*: 419 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-(2,4-difluorobenzylamino)-3-(2,2,2,trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.2 g, 5.26 mmol), to give the free base of the title compound as an oil (1.66 g, 98%) that solidified upon standing at room temperature and was used without further purification. MS (ES+) *m/z*: 323 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-(2,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.66 g, 5.14 mmol) to give the title compound as a white solid (2.03 g, 90%). MS (ES+) *m/z*: 323 $(M+H)^+$.

Example 538

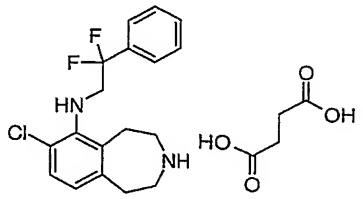
7-Chloro-6-(2,5-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Example 538 may be prepared essentially as described in Example 537 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,5-difluorobenzylamine (68% yield, MS (ES+) *m/z* 323 $(M+H)^+$).

Example 539

7-Chloro-6-(2,2-difluoro-2-phenyl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

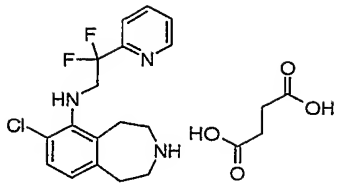


Use a method similar to the General Procedure 5-3 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (541 mg, 1.274 mmol), palladium(II) acetate (57 mg, 0.225 mmol), tris(dibenzylideneacetone)dipalladium(0) (117 mg, 0.127 mmol), BINAP (0.506 g, 0.764 mmol), 2,2-difluoro-2-phenyl-ethylamine (400 mg, 2.547 mmol) and cesium carbonate (830 mg, 2.548 mmol) in degassed toluene (35 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 16 h. Cool the mixture to room temperature, dilute with EtOAc and filter over Celite®. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to obtain 7-chloro-6-(2,2-difluoro-2-phenyl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (335 mg, 61%). MS (ES+) *m/z*: 433 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-(2,2-difluoro-2-phenyl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (317 mg, 0.734 mmol), to give the free base of the title compound as an oil (215 mg, 87%) that was used without further purification. MS (ES+) *m/z*: 337 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-(2,2-difluoro-2-phenyl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (215 mg, 0.64 mmol) to give the title compound as a white solid (220 mg, 76%). MS (ES+) *m/z*: 337 $(M+H)^+$.

Example 540

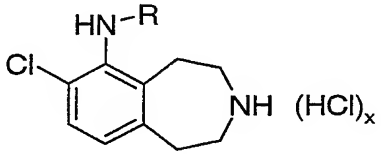
7-Chloro-6-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

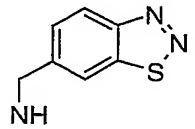
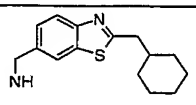
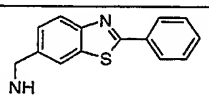
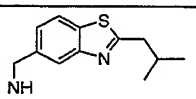


Example 540 may be prepared essentially as described in Example 539 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,2-difluoro-2-pyridin-2-yl-ethylamine (prepared by following the procedure described in *J. Med. Chem.* **2003**, *46*, 461-473), (37% yield, MS (ES+) *m/z* 338 $(M+H)^+$).

Examples 541-544

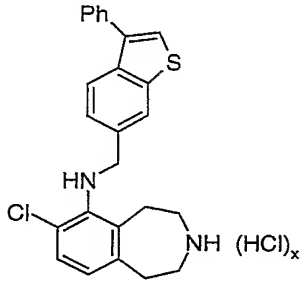
Examples 541-544 may be prepared essentially as described in Example 262 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
541		7-Chloro-6-(benzo[1,2,3]thiadiazol-6-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	12	345 $(M+H)^+$
542		7-Chloro-6-(2-cyclohexylmethyl-benzothiazol-6-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	50	441 $(M+H)^+$
543		7-Chloro-6-[(2-phenyl-benzothiazol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	27	420 $(M+H)^+$
544		7-Chloro-6-(2-isobutyl-benzothiazol-5-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	37	400 $(M+H)^+$

Example 545

7-Chloro-6-(3-phenyl-benzothiophen-6-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Hydrochloride

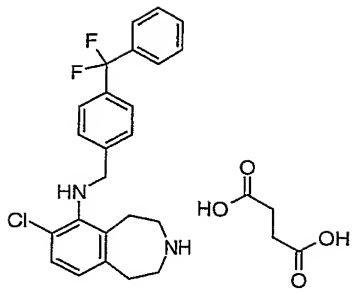


Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.28 g, 0.66 mmol) and 6-aminomethyl-3-phenyl-benzothiophene (0.19 g, 0.8 mmol) with tris(dibenzylideneacetone)dipalladium(0) (120 mg, 0.13 mmol), BINAP (165 mg, 0.26 mmol) and cesium carbonate (0.3 g, 0.93 mmol) at 90 °C for 17 h, to obtain 7-chloro-6-(3-phenyl-benzothiophen-6-yl-methylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine that is used without further purification (234 mg, 69%). MS (ES+) *m/z*: 515 (M+H)+.

Use a procedure similar to General Procedure 1-1 to deprotect 7-chloro-6-(3-phenyl-benzothiophen-6-yl-methylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine (234 mg, 0.45 mmol) in 7M ammonia in methanol (20 mL). Purify by reverse phase HPLC (Vydac C18 5 x 25 cm, 30% to 100% acetonitrile in 0.1% TFA-water solution). Recover the free base by SCX chromatography and form the salt according to General Procedure 2-3 to obtain the title compound (38 mg, 17%). HRMS (ES+) *m/z*: 419.1340 $(M+H)^+$.

Example 546

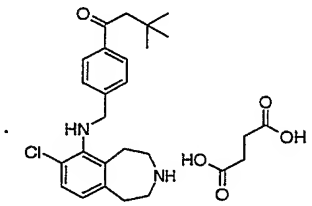
7-Chloro-6-[(difluoro-phenyl-methyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a procedure similar to Example 262 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(difluoro-phenyl-methyl)-benzylamine, followed by deprotection according to General Procedure 1-2 and salt formation according to General Procedure 2-1 to obtain the title compound (175 mg, 77%). MS (ES+) *m/z* 413 $(M+H)^+$.

Example 547

7-Chloro-6-[4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



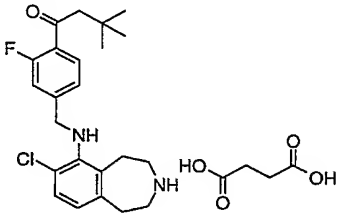
Use a method similar to the General Procedure 5-3 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.588 mmol), palladium(II) acetate (26 mg, 0.118 mmol), tris(dibenzylideneacetone)dipalladium(0) (53 mg, 0.059 mmol), BINAP (0.22 g, 0.353 mmol), 4-(3,3-dimethyl-butyryl)-benzylamine (241 mg, 1.176 mmol) and cesium carbonate (383 mg, 1.176 mmol) in degassed toluene (10 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 16 h. Cool the mixture to room temperature, dilute with EtOAc and wash with saturated aqueous $NaHCO_3$. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (90:10, 85:15) to obtain 7-chloro-6-[4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-

2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (185 mg, 65%). MS (ES+) *m/z*: 481 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (165 mg, 0.343 mmol), to give the free base of the title compound as an oil (130 mg, 98%) that was used without further purification. MS (ES+) *m/z*: 385 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (130 mg, 0.338 mmol) to give the title compound as a white solid (128 mg, 76%). MS (ES+) *m/z*: 385 $(M+H)^+$.

Example 548

7-Chloro-6-[4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

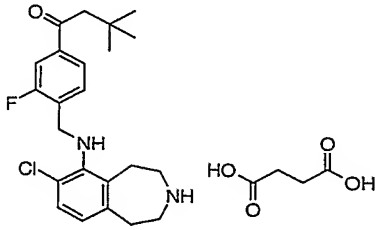


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (96 mg, 0.225 mmol) with 4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamine (105 mg, 0.45 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (41 mg, 0.045 mmol), BINAP (56 mg, 0.09 mmol) and cesium carbonate (103 mg, 0.315 mmol) in anhydrous toluene (15 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 7-chloro-6-[4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (54 mg, 49%). MS (ES+) *m/z*: 499 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (53 mg, 0.11 mmol) to give the free base of the title compound as a yellow oil (42 mg, 96%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (42 mg, 0.105 mmol) to give the title compound as a white solid (30 mg, 60%). MS (ES+) *m/z*: 403 $(M+H)^+$.

Example 549

7-Chloro-6-[4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



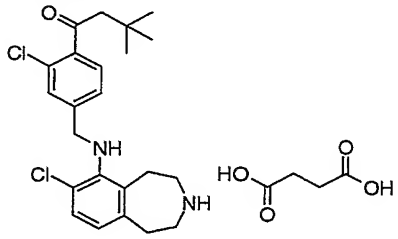
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (127 mg, 0.3 mmol) with 4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamine (120 mg, 0.54 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (27 mg, 0.03 mmol), BINAP (40 mg, 0.06 mmol) and cesium carbonate (137 mg, 0.42 mmol) in anhydrous toluene (20 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 and 9:1) followed by reverse phase HPLC [Zorbax Bonus RP, 5 □M 21.2 x 100 mm, eluting with water/acetonitrile (0.05% TFA in each) (35:65 to 15:85 gradient over 5 min), flow rate 25 mL/min, UV detector (230 nm)] to give 7-chloro-6-[4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (72 mg, 49%). MS (ES+) *m/z*: 499 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine (26 mg, 0.052 mmol) to give the free base of the title compound as a yellow oil (19 mg, 91%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(3,3-dimethyl-butyryl)-2-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (18 mg, 0.045 mmol) to give the title compound as a white solid (20 mg, 86%). MS (ES+)m/z: 403 $(M+H)^+$.

Example 550

7-Chloro-6-[3-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



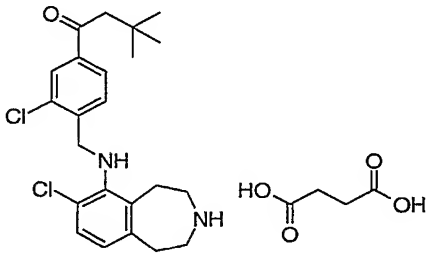
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (90 mg, 0.212 mmol) with 3-chloro-4-(3,3-dimethyl-butyryl)-benzylamine (102 mg, 0.43 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (39 mg, 0.0424 mmol), BINAP (53 mg, 0.0848 mmol) and cesium carbonate (97 mg, 0.297 mmol) in anhydrous toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 7-chloro-6-[3-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (72 mg, 49%). MS (ES+) *m/z*: 516 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[3-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 0.136 mmol) to give the free base of the title compound as a yellow oil (57 mg, 99%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[3-chloro-4-(3,3-dimethyl-butyryl)-

benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (57 mg, 0.136 mmol) to give the title compound as a white solid (50 mg, 68%). MS (ES+) *m/z*: 420 $(M+H)^+$.

Example 551

7-Chloro-6-[2-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

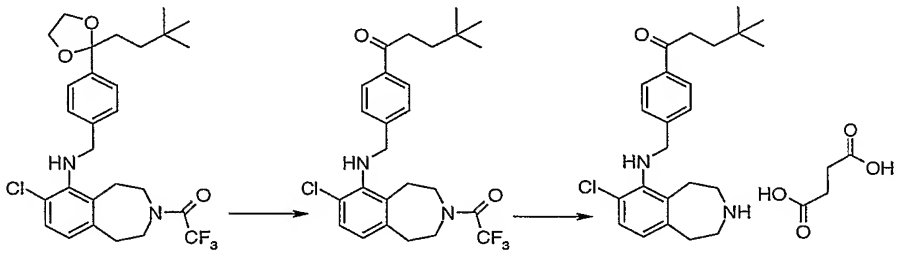


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.71 mmol) with 1-(4-aminomethyl-3-chloro-phenyl)-3,3-dimethyl-butan-1-one (338 mg, 1.41 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (130 mg, 0.142 mmol), BINAP (177 mg, 0.284 mmol) and cesium carbonate (324 mg, 0.994 mmol) in anhydrous toluene (31 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (92:8) followed by reverse phase HPLC [Hichrom Kromasil C18, 5 □M 21.2 x 100 mm, eluting with water/acetonitrile (0.05% TFA in each) (1:4 to 1:19 gradient over 5 min), flow rate 25 mL/min, UV detector (230 nm)] to give 7-chloro-6-[2-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (77 mg, 21%). MS (ES+) *m/z*: 516 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[2-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (77 mg, 0.15 mmol) to give the free base of the title compound as a yellow oil (93 mg, 99%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[2-chloro-4-(3,3-dimethyl-butyryl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (63 mg, 0.15 mmol) to give the title compound as a white solid (52 mg, 65%). MS (ES+) *m/z*: 420 $(M+H)^+$.

Example 552

7-Chloro-6-[4-(4,4-dimethyl-pentanoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-2 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (233 mg, 0.55 mmol), tris(dibenzylideneacetone)dipalladium(0) (50 mg, 0.055 mmol), BINAP (73 mg, 0.11 mmol), 4-[2-(3,3-dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine (263 mg, 1 mmol) and cesium carbonate (250 mg, 0.77 mmol) in degassed toluene (20 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 14 h. Cool the mixture to room temperature, dilute with EtOAc and filter through Celite®. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (19:1, 9:1 and 4:1) to obtain 7-chloro-6-{4-[2-(3,3-dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (185 mg, 63%). MS (ES+) *m/z*: 539 $(M+H)^+$.

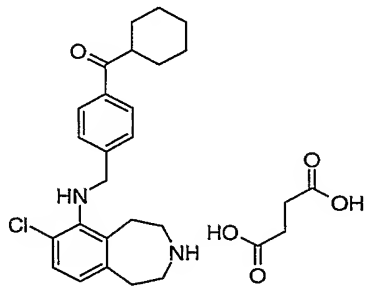
Dissolve 7-chloro-6-{4-[2-(3,3-dimethyl-butyl)-[1,3]dioxolan-2-yl]-benzylamine}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (185 mg, 0.34 mmol) in methanol (10 mL) and add 1N aqueos HCl (2 mL). Stir the mixture for 2 h and concentrate *in vacuo*. Dissolve the residue in dichloromethane and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo* to obtain 7-chloro-6-[4-(4,4-dimethyl-pentanoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (150 mg, 89%).

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(4,4-dimethyl-pentanoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine (150 mg, 0.3 mmol), to give the free base of the title compound as an oil (100 mg, 83%) that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(4,4-dimethyl-pentanoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.25 mmol) to give the title compound as a solid (100 mg, 78%). MS (ES+) *m/z*: 399 $(M+H)^+$.

Example 553

7-Chloro-6-(4-cyclohexanecarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



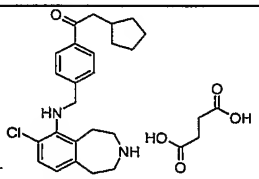
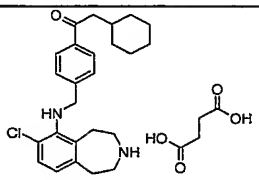
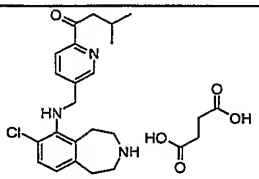
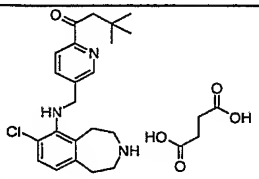
Use a method similar to the General Procedure 5-2 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.353 mmol), tris(dibenzylideneacetone)dipalladium(0) (64 mg, 0.071 mmol), BINAP (88 mg, 0.141 mmol), 4-cyclohexanecarbonyl-benzylamine (125 mg, 0.576 mmol) and cesium carbonate (230 mg, 0.706 mmol) in degassed toluene (10 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 6 h. Cool the mixture to room temperature, dilute with EtOAc and filter through Celite®. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (90:10 and 85:15) to obtain 7-chloro-6-(4-cyclohexanecarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (130 mg, 75%). MS (ES+) *m/z*: 493 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-(4-cyclohexanecarbonyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (120 mg, 0.243 mmol), to give the free base of the title compound as an oil (86 mg, 89%) that was used without further purification. MS (ES+) *m/z*: 397 $(M+H)^+$.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-(4-cyclohexanecarbonyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (86 mg, 0.217 mmol) to give the title compound as a solid (85 mg, 77%). MS (ES+) *m/z*: 397 $(M+H)^+$.

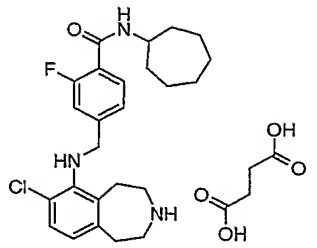
Examples 554-557

Examples 554-557 may be prepared essentially as described in Example 553 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
554		7-Chloro-6-[4-(2-cyclopentyl-acetyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	64	397 $(M+H)^+$
555		7-Chloro-6-[4-(2-cyclohexyl-acetyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	30	411 $(M+H)^+$
556		7-Chloro-6-[6-(3-methyl-butyryl)-pyridin-3-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	35	372 $(M+H)^+$
557		7-Chloro-6-[6-(3,3-dimethyl-butyryl)-pyridin-3-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	30	386 $(M+H)^+$

Example 558

7-Chloro-6-(4-cycloheptylcarbamoyl-3-fluoro-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

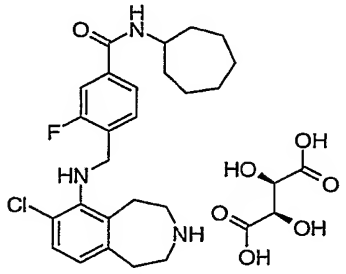


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 2.5 mmol) with 4-aminomethyl-*N*-cycloheptyl-2-fluoro-benzamide (1.35 g, 5.1 mmol) in anhydrous toluene (25 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 1:1 gradient) followed by SCX chromatography to obtain 7-chloro-6-[4-cycloheptylcarbamoyl-3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (720 mg, 53%). MS (ES+) *m/z*: 540.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-[4-cycloheptylcarbamoyl-3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (665 mg, 89%). MS (ES+) *m/z*: 444.2 $(M+H)^+$.

Example 559

7-Chloro-6-(4-cycloheptylcarbamoyl-2-fluoro-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



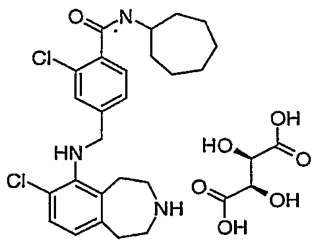
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

(640 mg, 1.5 mmol) with 4-aminomethyl-*N*-cycloheptyl-3-fluoro-benzamide (795 mg, 3 mmol) in anhydrous toluene (20 mL). Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:2 gradient) to obtain 7-chloro-6-(4-cycloheptylcarbamoyl-2-fluoro-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (568 mg, 70%). MS (ES+) *m/z*: 540.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-(4-cycloheptylcarbamoyl-2-fluoro-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99/1 to 93/7 gradient) to give the free base of the title compound. Dissolve the free base (400 mg, 0.9 mmol) and *L*-tartaric acid (135 mg, 0.9 mmol) in methanol. Concentrate *in vacuo* to an oil. Triturate oil with dichloromethane and remove solvent *in vacuo* to obtain the title compound as a solid (460 mg, 74%). MS (ES+) *m/z*: 444.2 $(M+H)^+$.

Example 560

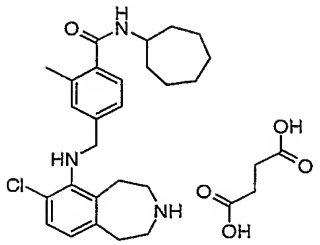
7-Chloro-6-(3-chloro-4-cycloheptylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



Example 560 may be prepared essentially as described in Example 559 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-aminomethyl-2-chloro-*N*-cycloheptyl-benzamide (50% yield, MS (ES+) *m/z* 460.2 $(M+H)^+$).

Example 561

7-Chloro-6-(4-cycloheptylcarbamoyl-3-methyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

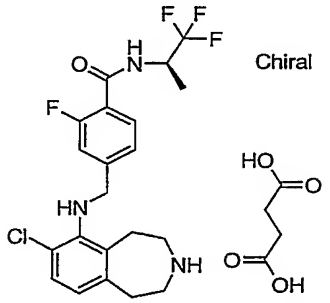


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (660 mg, 1.6 mmol) with 4-aminomethyl-*N*-cycloheptyl-2-methyl-benzamide (810 mg, 3.1 mmol) in anhydrous toluene (18 mL). Purify the crude mixture by chromatography on silica gel eluting with hexane/THF (19:1 to 7:3 gradient) to obtain 7-chloro-6-(4-cycloheptylcarbamoyl-3-methyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (690 mg, 83%). MS (ES+) *m/z*: 536.3 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-(4-cycloheptylcarbamoyl-3-methyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (680 mg, 1.3 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 97:3 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (473 mg, 65%). MS (ES+) *m/z*: 440.3 $(M+H)^+$.

Example 562

(*R*)-7-Chloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-methyl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



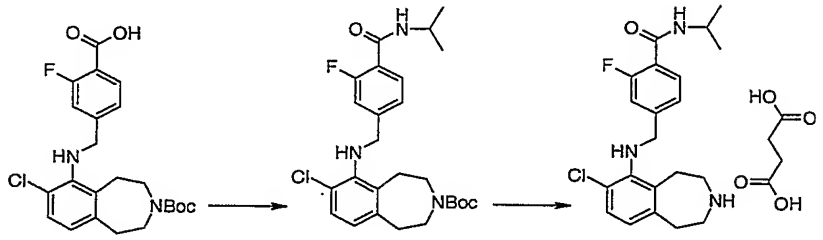
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

(0.561 g, 1.319 mmol) with (*R*)-4-aminomethyl-2-fluoro-*N*-(2,2,2-trifluoro-1-methyl-ethyl)-benzamide (0.698 g, 2.642 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (0.241 g, 0.264 mmol), BINAP (0.33 g, 0.53 mmol) and cesium carbonate (1.51 g, 4.63 mmol) in anhydrous toluene (13 mL). Purify by chromatography on silica gel (40 g RediSep® column) eluting with hexane/EtOAc (19:1 to 1:1 gradient over 30 min; 35 mL/min) and then by SCX chromatography to afford (*R*)-7-chloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-methyl-ethylcarbamoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (0.444 g, 62%). MS (ES+) *m/z*: 540.1 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect (*R*)-7-chloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-methyl-ethylcarbamoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.224 g, 0.415 mmol). Purify by chromatography on silica gel (12 g RediSep® column) eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient over 30 min; 35 mL/min) to afford the free base of the title compound as a white foam (0.142 g, 77%). Use a method similar to the General Procedure 2-1, using (*R*)-7-chloro-6-[3-fluoro-4-(2,2,2-trifluoro-1-methyl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.132 g, 0.299 mmol) to afford the title compound as a white solid (0.135 g, 80%). MS (ES+) *m/z*: 444.2 $(M+H)^+$.

Example 563

7-Chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



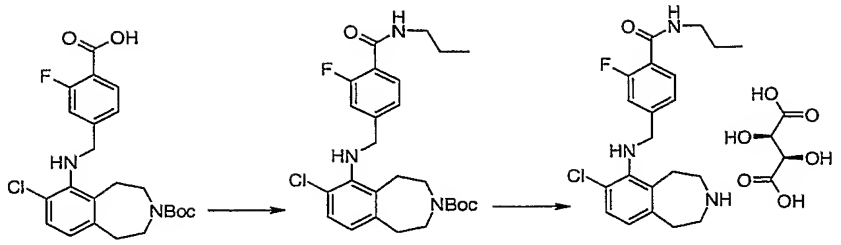
Add isopropylamine (0.15 mL, 1.8 mmol), HOBT (0.24 g, 1.8 mmol), diisopropylethylamine (0.63 mL, 3.6 mmol) and EDC (0.34 g, 1.8 mmol) to a mixture of

3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.403 g, 0.9 mmol) in anhydrous THF (11.8 mL) at room temperature. Stir overnight at room temperature and partition the mixture between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (100 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel (40 g RediSep® column) eluting with hexane/EtOAc (19:1 to 1:1 gradient over 30 min; 50 mL/min) to afford 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a thick colorless oil (0.439 g, 100%). MS (ES+) *m/z*: 490.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.406 g, 0.83 mmol) in 1,4-dioxane (12.8 mL). Purify by SCX chromatography eluting with dichloromethane and dichloromethane/2M ammonia in methanol (1:1) followed by chromatography on silica gel (40 g RediSep column) eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 over 30 min) and then dichloromethane/2M ammonia in methanol (90:10 over 30 min; 35 mL/min) to afford 7-chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (0.3237 g). MS (ES+) *m/z*: 390.1 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-(3-fluoro-4-isopropylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.301 g, 0.772 mmol) to provide the title compound as a beige solid (0.328 g, 84%). MS (ES+) *m/z*: 390.1 $(M+H)^+$.

Example 564

7-Chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

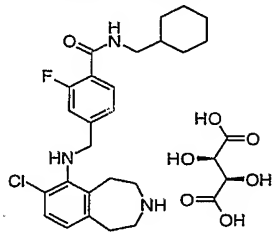


Add a solution of *n*-propylamine (6.3 mg, 0.11 mmol) in anhydrous THF (0.5 mL), HOBT (14.5 mg, 0.11 mmol), a solution of diisopropylamine (27.7 mg, 0.21 mmol) in anhydrous THF (0.5 mL) and EDC (20.5 mg, 0.11 mmol) to a mixture of 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (48.1 mg, 0.11 mmol) in anhydrous THF (1.4 mL) at room temperature. Stir overnight at room temperature and partition the mixture between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (20 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel (12 g RediSep® column) eluting with hexane/EtOAc (19:1 to 1:1 gradient over 30 min; 35 mL/min) to afford 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a thick colorless oil (37.1 mg, 71%). MS (ES+) *m/z*: 490.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (33.1 mg, 0.83 mmol) in 1,4-dioxane (1 mL). Purify by SCX chromatography eluting with dichloromethane and dichloromethane/2M ammonia in methanol (1:1) to afford 7-chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (25.2 mg, 96%). MS (ES+) *m/z*: 390.1 $(M+H)^+$. Use a method similar to the General Procedure 2-6, using 7-chloro-6-(3-fluoro-4-propylcarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (25 mg, 0.064 mmol) to provide the title compound as a white foam (31.4 mg, 91%). MS (ES+) *m/z*: 390.1 $(M+H)^+$.

Example 565

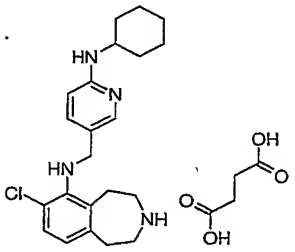
7-Chloro-6-[4-(cyclohexylmethylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



Example 565 may be prepared essentially as described in Example 564 by using 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and cyclohexylmethylamine (67% yield, MS (ES+) *m/z* 444 $(M+H)^+$).

Example 566

7-Chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

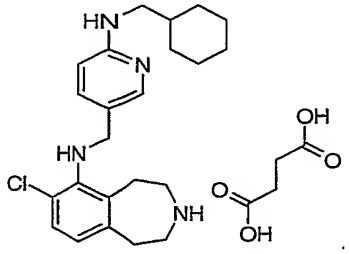


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (800 mg, 1.9 mmol) with 5-aminomethyl-2-cyclohexylamino-pyridine (910 mg, 4.4 mmol) in anhydrous toluene (15 mL). Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:2 gradient) to obtain 7-chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (520 mg, 58%). MS (ES+) *m/z*: 481.0 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99/1 to 85/15 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (360 mg, 66%). MS (ES+) *m/z*: 385.1 $(M+H)^+$.

Example 567

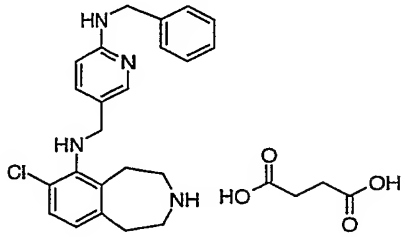
7-Chloro-6-(6-cyclohexylmethylamino-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



The title compound may be prepared essentially as described in Example 566 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-aminomethyl-2-cyclohexylmethylamino-pyridine (22% yield, MS (ES+) *m/z* 399.1 $(M+H)^+$).

Example 568

6-[6-(Benzylamino)-pyridin-3-ylmethylamino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

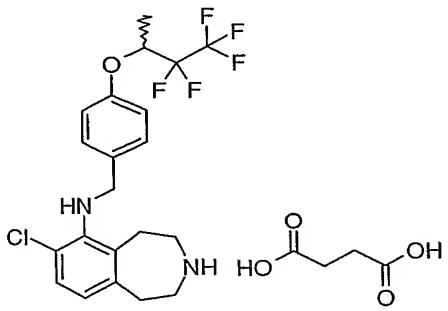


Use a method similar to General Procedure 5-2 to couple 6-benzylamino-pyridin-3-ylmethylamine and 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-

2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection and salt formation by methods similar to the General Procedures 1-3 and 2-1, the title compound as an off-white solid (45% overall yield). HRMS (ES+) *m/z*: 393.1836 $(M+H)^+$.

Example 569

(±)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

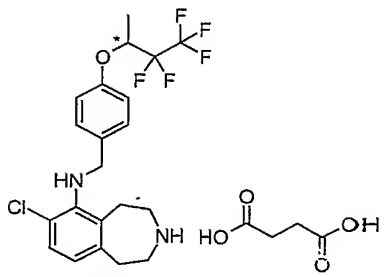


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (751 mg, 1.8 mmol) with (±)-4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamine (950 mg, 3.5 mmol) in anhydrous toluene (20 mL). Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane/EtOAc (10:1, 5:1, 3:1) to obtain (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (990 mg, 99%).

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (980 mg, 1.8 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (650 mg, 64%). MS (ES+) *m/z*: 449.1 $(M+H)^+$.

Example 570

(-)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



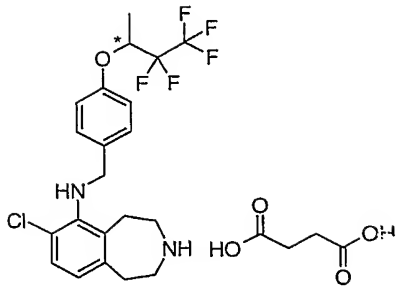
Chiral

Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (9 g, 21.1 mmol) with 4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamine isomer 2 (11.4 g, 42.3 mmol) in anhydrous toluene (270 mL). Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 4:1 gradient) to obtain 7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 2 (9.5 g, 83%).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 2 (9.5 g, 17.4 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (5.9 g, 60%). MS (ES+) *m/z*: 449.1 $(M+H)^+$. $[\alpha]^{20}_D$ –11.6° (c 0.5, MeOH).

Example 571

(+)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



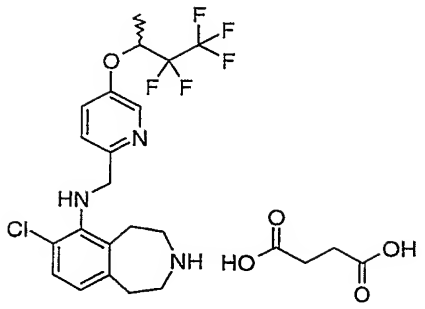
Chiral

Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.4 g, 8 mmol) with 4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamine isomer 1 (4.3 g, 16 mmol) in anhydrous toluene (100 mL). Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:1 gradient) to obtain 7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 1 (3.7 g, 85%).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 1 (3.7 g, 6.8 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 97:3 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (2.8 g, 74%). MS (ES+) *m/z*: 449.1 $(M+H)^+$. $[\alpha]^{20}_D$ +13.0° (c 0.5, MeOH).

Example 572

(±)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

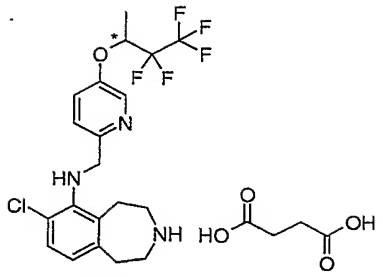


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (268 mg, 0.6 mmol) with (±)-2-aminomethyl-5-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridine (170 mg, 0.6 mmol) in anhydrous toluene (3 mL). Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane/EtOAc (10:1, 5:1, 3:1) to obtain (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (270 mg, 79%). MS (ES+) *m/z*: 546.1 $(M+H)^+$.

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (265 mg, 0.5 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (172 mg, 63%). MS (ES+) *m/z*: 450.1 $(M+H)^+$.

Example 573

(-)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

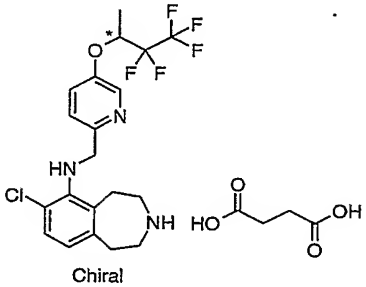


Chiral

Separate (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate (172 mg) by normal phase chiral chromatography (Chiralcel OD, 8 x 35 cm, eluting with heptane/isopropanol 4:1 with 0.2% DMEA). Collect the 1st eluting isomer, then use a method similar to the General Procedure 2-1 to obtain the title compound [50 mg, 96.3% ee (Chiralcel OD-H, 4.6 x 150 mm, eluting with heptane/isopropanol 4:1 with 0.2% DMEA, 0.6 mL/min)]. MS (ES+) *m/z*: 450.1 $(M+H)^+$. $[\alpha]^{20}_D$ –10.5° (c 0.5, MeOH).

Example 574

(+)-7-Chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

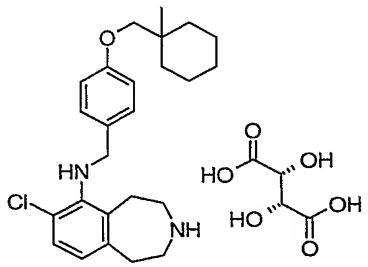


Chiral

Separate (±)-7-chloro-6-{4-[1-(1,1,2,2,2-pentafluoroethyl)-ethoxy]-pyridin-2-ylmethylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate (172 mg) by normal phase chiral chromatography (Chiralcel OD, 8 x 35 cm, eluting with heptane/isopropanol 4:1 with 0.2% DMEA). Collect the 2nd eluting isomer, then use a method similar to the General Procedure 2-1 to obtain the title compound [41 mg, 95.6% ee (Chiralcel OD-H, 4.6 x 150 mm, eluting with heptane/isopropanol 4:1 with 0.2% DMEA, 0.6 mL/min)]. MS (ES+) *m/z*: 450.1 $(M+H)^+$. $[\alpha]^{20}_D$ +13.1° (c 0.5, MeOH).

Example 575

7-Chloro-6-[4-(1-methyl-cyclohexylmethoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

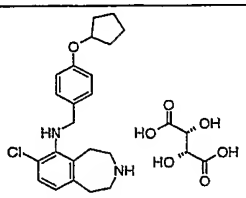
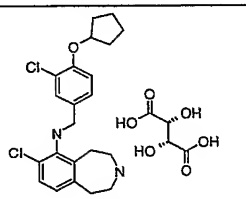
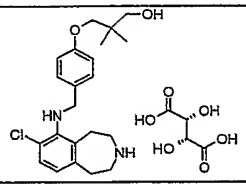
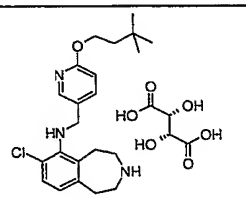
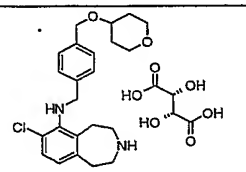


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) with 4-(1-methyl-cyclohexylmethoxy)-benzylamine (120 mg, 0.51 mmol) in anhydrous 1,4-dioxane (7 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (19:1 to 4:1 gradient) to obtain 7-chloro-6-[4-(1-methyl-cyclohexylmethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (101 mg, 39%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[4-(1-methyl-cyclohexylmethoxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.19 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-6 to obtain the title compound (78 mg, 73%). MS (ES+) *m/z*: 413.2 $(M+H)^+$.

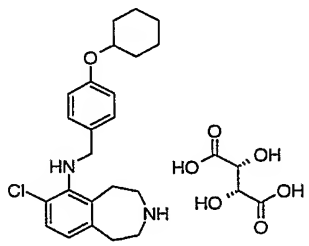
Examples 576-580

Examples 576-580 may be prepared essentially as described in Example 575 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
576		7-Chloro-6-(4-cyclopentyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	39	371 $(M+H)^+$
577		7-Chloro-6-(3-chloro-4-cyclopentyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	6	405 $(M+H)^+$
578		7-Chloro-6-[4-(2,2,dimethyl-3-hydroxy-propoxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	6	389 $(M+H)^+$
579		7-Chloro-6-[6-(3,3-dimethyl-butoxy)-pyridin-3-ylmethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	50	388 $(M+H)^+$
580		7-Chloro-6-[4-(tetrahydro-pyran-4-yloxymethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	37	401 $(M+H)^+$

Example 581

7-Chloro-6-(4-cyclohexyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

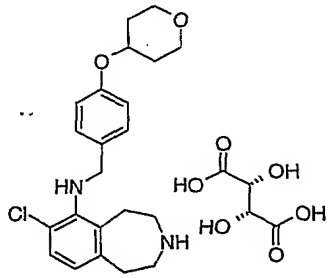


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.43 mmol) with 4-cyclohexyloxy-benzylamine (58 mg, 0.285 mol) in anhydrous toluene (1 mL). Purify the crude mixture by chromatography on silica gel eluting with cyclohexane/EtOAc (9:1) to give 7-chloro-6-(4-cyclohexyloxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (78 mg, 69%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(4-cyclohexyloxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (237 mg, 0.49 mmol) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-6 to obtain the title compound (208 mg, 80%). MS (ES+) *m/z*: 385.2 $(M+H)^+$.

Example 582

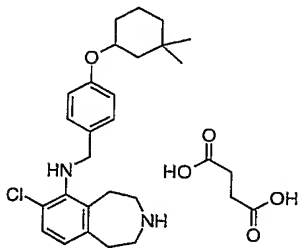
7-Chloro-6-[4-(tetrahydro-pyran-4-yloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate



Example 582 may be prepared essentially as described in Example 581 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(tetrahydro-pyran-4-yloxy)-benzylamine (4% yield, MS (ES+) *m/z* 387 $(M+H)^+$).

Example 583

(±)-7-Chloro-6-[4-(3,3-dimethyl-cyclohexyloxy)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

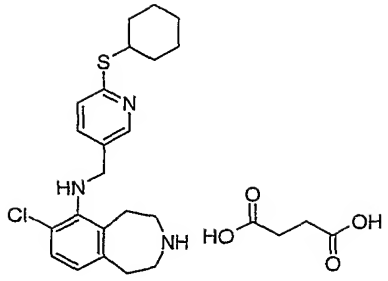


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (387 mg, 0.91 mmol) with (±)-4-(3,3-dimethyl-cyclohexyloxy)-benzylamine (233 mg, 1 mmol) in anhydrous 1,4-dioxane (14 mL). Purify the crude mixture by chromatography on silica gel eluting with cyclohexane/EtOAc (19:1 to 1:1 gradient) to obtain (±)-7-chloro-6-[4-(3,3-dimethyl-cyclohexyloxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (227 mg, 50%).

Use a method similar to the General Procedure 1-1 to deprotect (±)-7-chloro-6-[4-(3,3-dimethyl-cyclohexyloxy)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (220 mg, 0.43 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Further purify the residue by preparative HPLC. Use a method similar to the General Procedure 2-1 to obtain the title compound (65 mg, 13%). MS (ES+) *m/z*: 413.2 $(M+H)^+$.

Example 584

7-Chloro-6-(4-cyclohexylthio-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

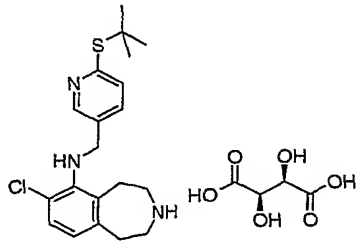


Add cesium carbonate (2.04 g, 6.27 mmol), palladium(II) acetate (46 mg, 0.209 mmol) and BINAP (195.21 mg, 0.313 mmol) to a solution of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.79 g, 4.18 mmol) and 5-aminomethyl-2-cyclohexylthio-pyridine (1.11 g, 5.02 mmol) in anhydrous toluene (30 mL). Sonicate the resulting suspension for 30 min then heat at 100 °C for 18 h. Cool the reaction to room temperature. Purify the crude mixture by chromatography on silica gel eluting with cyclohexane/EtOAc (98:2 to 60:40 gradient) to give 7-chloro-6-(4-cyclohexylthio-pyridin-3-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (1.1 g, 53%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(4-cyclohexylthio-pyridin-3-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 2.21 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (0.884 g, 77%). MS (ES+) *m/z*: 402 $(M+H)^+$.

Example 585

6-(4-*tert*-Butylthio-pyridin-3-ylmethylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-tartrate

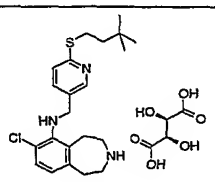
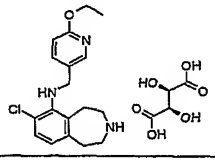


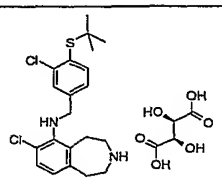
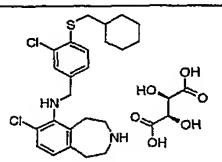
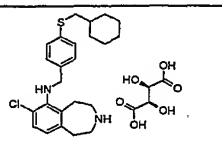
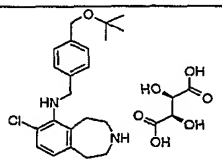
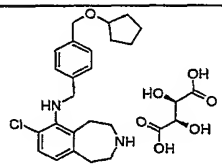
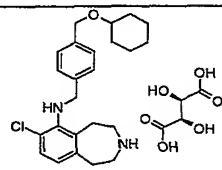
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (990 mg, 2.32 mmol) with 5-aminomethyl-2-*tert*-butylthio-pyridine (500 mg, 2.55 mmol) in anhydrous toluene (15 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 3:1 gradient) to obtain 6-(4-*tert*-butylthio-pyridin-3-ylmethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (650 mg, 59%). MS (ES+) *m/z*: 472 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 6-(4-*tert*-butylthio-pyridin-3-ylmethylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (650 mg, 1.37 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-6 to obtain the title compound (362 mg, 50%). MS (ES+) *m/z*: 376 $(M+H)^+$.

Examples 586-593

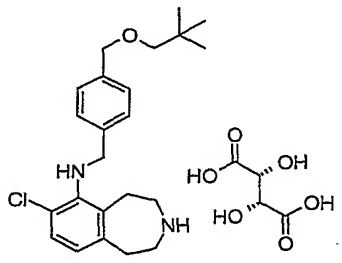
Examples 586-593 may be prepared essentially as described in Example 585 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
586		7-Chloro-6-[4-(3,3-dimethylbutylthio)-pyridin-3-ylmethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	25	404 $(M+H)^+$
587		7-Chloro-6-(4-ethoxy-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	30	332 $(M+H)^+$

588		6-(4-*tert*-Butylthio-3-chloro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	37	409 $(M+H)^+$
589		7-Chloro-6-(3-chloro-4-cyclohexylmethylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	27	472 $(M+Na)^+$
590		7-Chloro-6-(4-cyclohexylmethylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	13	415 $(M+H)^+$
591		6-(4-*tert*-Butoxymethyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	16	373 $(M+H)^+$
592		7-Chloro-6-(4-cyclopentyloxymethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	39	385 $(M+H)^+$
593		7-Chloro-6-(4-cyclohexyloxymethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	33	399 $(M+H)^+$

Example 594

7-Chloro-6-[4-(2,2-dimethyl-propoxymethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

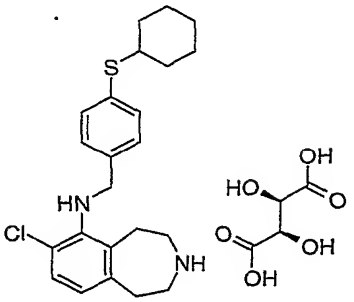


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1 mmol) with 4-(2,2-dimethyl-propoxymethyl)-benzylamine (230 mg, 1.1 mmol) in anhydrous toluene (20 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 4:1 gradient) to obtain 7-chloro-6-[4-(2,2-dimethyl-propoxymethyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (380 mg, 79%). MS (ES+) *m/z*: 483 $(M+H)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-[4-(2,2-dimethyl-propoxymethyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (380 mg, 0.88 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-6 to obtain the title compound (319.2 mg, 70%). MS (ES+) *m/z*: 387 $(M+H)^+$.

Example 595

7-Chloro-6-(4-cyclohexylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

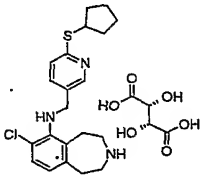
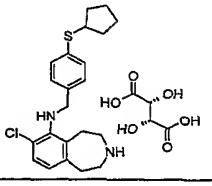


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (167 mg, 0.392 mmol) with 4-cyclohexylthio-benzylamine (95.4 mg, 0.431 mmol) in anhydrous 1,4-dioxane (5 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 13:7 gradient) to obtain 7-chloro-6-(4-cyclohexylthio-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (155 mg, 79%). MS (ES+) *m/z*: 519 $(M+Na)^+$.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-6-(4-cyclohexylthio-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (155 mg, 0.312 mmol). Purify by SCX chromatography eluting with methanol and 3M ammonia in methanol. Use a method similar to the General Procedure 2-6 to obtain the title compound (95 mg, 75%). MS (ES+) *m/z*: 401 $(M+H)^+$.

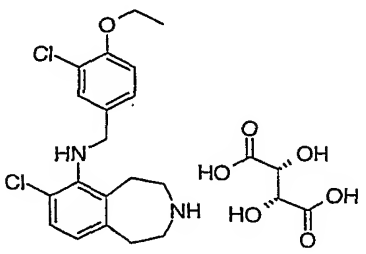
Examples 596-597

Examples 596-597 may be prepared essentially as described in Example 595 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
596		7-Chloro-6-(4-cyclopentylthio-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	58	388 $(M+H)^+$
597		7-Chloro-6-(4-cyclopentylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate	66	387 $(M+H)^+$

Example 598

7-Chloro-6-(3-chloro-4-ethoxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

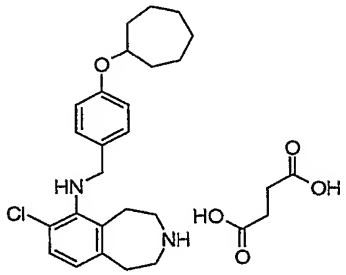


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.35 mmol) with 4-ethoxy-3-chloro-benzylamine (94.7 mg, 0.51 mmol) in anhydrous 1,4-dioxane (10 mL). Purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (100:0 to 77:23 gradient) to obtain 7-chloro-6-(3-chloro-4-ethoxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (111.3 mg, 68%). MS (ES+) *m/z*: 483 $(M+Na)^+$.

Use a method similar to the General Procedure 1-1, but adding water (10 mL) to the 7M ammonia in methanol solution (20 mL), to deprotect 7-chloro-6-(3-chloro-4-ethoxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (27 mg, 0.072 mmol) to give the free base of the title compound. Use a method similar to the General Procedure 2-6 to give the title compound as a solid (29 mg, 78%). MS (ES+) *m/z*: 365 $(M+H)^+$.

Example 599

7-Chloro-6-(4-cycloheptyloxy-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



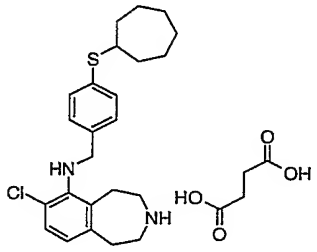
Under a nitrogen atmosphere, add 4-cycloheptyloxy-benzylamine (451 mg, 2.06 mmol), 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.17 mmol), palladium(II) acetate (26 mg, 0.117 mmol), BINAP (110 mg, 0.176 mmol), and cesium carbonate (1.15 g, 3.52 mmol) to toluene (20 mL). Heat the mixture at 90 °C for 12 h. Cool the mixture to room temperature and dilute with EtOAc (25 mL). Filter the solids through cellulose (20 g) and

concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (45 g RediSep column) eluting with hexane/EtOAc (1:0 to 4:1 gradient over 1 h; 80 mL/min) to provide 7-chloro-6-(4-cycloheptyloxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (384 mg, 61%). MS (APCI) *m/z*: 495 $(M+H)^+$.

Dissolve 7-chloro-6-(4-cycloheptyloxy-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (370 mg, 0.747 mmol) and lithium hydroxide monohydrate (153 mg, 3.73 mmol) in methanol (5 mL) and stir for 6 h. Concentrate the mixture *in vacuo* and dissolve the residue in water (20 mL). Extract the mixture with EtOAc (3 × 20 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by reverse phase HPLC [Phenomonex C18(2) column, 5 × 25 cm, eluting with a gradient of water/acetonitrile (0.1% TFA in each) (9:1 through 1:9 over 40 min), 118 mL/min] to provide the trifluoroacetate salt of the title compound. Dissolve the residue in methanol and elute through an SCX column with saturated ammonia in methanol to provide the free base of the title compound (197 mg, 65%). Use a method similar to the General Procedure 2-1 to give the title compound as an off-white solid (250 mg, 100%). MS (APCI) *m/z*: 399 $(M+H)^+$.

Example 600

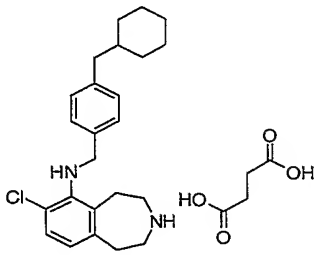
7-Chloro-6-(4-cycloheptylthio-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Example 600 may be prepared essentially as described in Example 599 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-cycloheptylthio-benzylamine (6% yield, MS (ES+) *m/z* 415 $(M+H)^+$).

Example 601

7-Chloro-6-(4-cyclohexylmethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



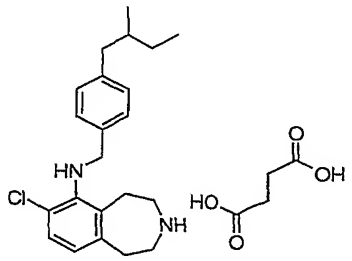
Under a nitrogen atmosphere, add 4-cyclohexylmethyl-benzylamine hydrochloride (352 mg, 1.47 mmol), 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.17 mmol), palladium(II) acetate (52.7 mg, 0.235 mmol), BINAP (293 mg, 0.47 mmol) and cesium carbonate (1.53 g, 4.7 mmol) to toluene (20 mL). Heat the mixture at 90 °C for 12 h. Cool the mixture to room temperature and dilute with EtOAc (25 mL). Filter the solids through cellulose (20 g) and concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (45 g RediSep column) eluting with hexane/EtOAc (1:0 to 4:1 gradient over 1 h; 80 mL/min) to provide 7-chloro-6-(4-cyclohexylmethyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (354 mg, 63%). MS (APCI) *m/z*: 479 $(M+H)^+$.

Dissolve 7-chloro-6-(4-cyclohexylmethyl-benzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (354 mg, 0.739 mmol) and lithium hydroxide monohydrate (100 mg, 2.43 mmol) in methanol (5 mL) and stir overnight. Concentrate the mixture *in vacuo* and dissolve the residue in water (20 mL). Extract the mixture with EtOAc (3 × 20 mL). Dry the combined organic extracts over Na_2SO_4, filter, and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel (40 g RediSep column) eluting with a gradient of dichloromethane and chloroform/methanol/concentrated ammonium hydroxide (80:18:2) over 1 h (80 mL/min) followed by reverse phase HPLC [Phenomonex C18(2) column (5 × 25 cm), eluting with water/acetonitrile (0.1% TFA in each) (9:1 to 1:9 gradient over 40 min), 118 mL/min] to obtain the trifluoroacetate salt of the title compound. Dissolve the residue in methanol

and elute through SCX column with saturated ammonia in methanol to provide 7-chloro-6-(4-cyclohexylmethyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (184 mg, 64%). Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (240 mg, 100%). MS (ES) *m/z*: 383 $(M+H)^+$.

Example 602

7-Chloro-6-[4-(2-methyl-butyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



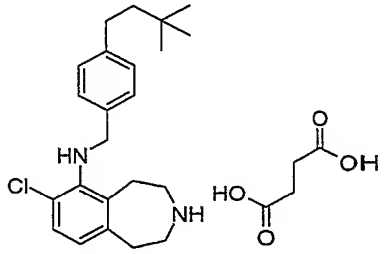
Under a nitrogen atmosphere, add 4-(2-methyl-butyl)-benzylamine (450 mg, 2.54 mmol), 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (720 mg, 1.7 mmol), palladium(II) acetate (40 mg, 0.17 mmol), BINAP (222 mg, 0.34 mmol) and cesium carbonate (1.4 g, 4.3 mmol) to toluene (20 mL). Heat the mixture at 95 °C for 12 h. Cool the mixture to room temperature and apply the mixture to a silica gel column eluting with hexane/EtOAc (10:1) to provide 7-chloro-6-[4-(2-methyl-butyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (450 mg, 59%). MS (ES+) *m/z*: 453 $(M+H)^+$.

Dissolve 7-chloro-6-[4-(2-methyl-butyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (450 mg, 1 mmol) and concentrated ammonium hydroxide (5 mL) in methanol (10 mL) and stir overnight. Concentrate the mixture *in vacuo*. Purify the crude mixture by SCX chromatography eluting with methanol and 3M ammonia in methanol. Concentrate the product *in vacuo* and purify the residue by reverse phase HPLC [Phenomonex Luna C18(2), 50 mm × 250 mm, eluting with acetonitrile/water with 0.1% TFA (2:3)]. Concentrate *in vacuo*, basify with potassium carbonate and extract into dichloromethane. Dry the organic solution over Na_2SO_4, filter

and concentrate *in vacuo* to provide the free base of the title compound (205 mg, 57%). Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (280 mg, 59%). MS (APCI) *m/z*: 357 $(M+H)^+$.

Example 603

7-Chloro-6-[4-(3,3-dimethyl-butyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



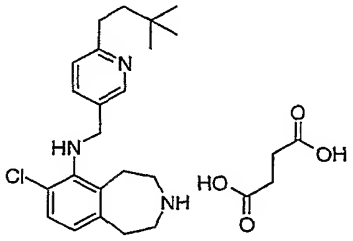
Use a method similar to the General Procedure 5-1 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (623 mg, 1.46 mmol), palladium(II) acetate (33 mg, 0.146 mmol), BINAP (182 mg, 0.292 mmol), 4-(3,3-dimethyl-butyl)-benzylamine (560 mg, 2.93 mmol) and cesium carbonate (666 mg, 2.04 mmol) in degassed toluene (40 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 16 h. Cool the mixture to room temperature, dilute with EtOAc and wash with water. Dry the organic phase over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (19:1, 9:1) to obtain 7-chloro-6-[4-(3,3-dimethyl-butyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (622 mg, 91%). MS (ES+) *m/z*: 467 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(3,3-dimethyl-butyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (448 mg, 0.96 mmol), to give the free base of the title compound as an oil (320 mg, 90%) that was used without further purification. MS (ES+) *m/z*: 371 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[4-(3,3-dimethyl-butyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (315 mg, 0.85

mmol) to give the title compound as a white solid (340 mg, 82%). MS (ES+) *m/z*: 371 $(M+H)^+$.

Example 604

7-Chloro-6-[6-(3,3-dimethyl-butyl)-pyridin-3-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

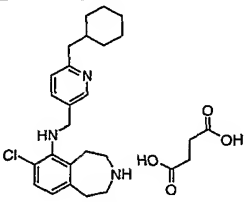
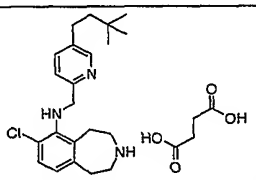
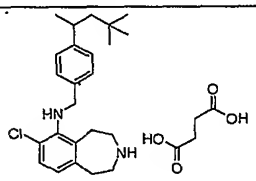


Use a method similar to the General Procedure 5-2 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (166 mg, 0.39 mmol), tris(dibenzylideneacetone)dipalladium(0) (71 mg, 0.078 mmol), BINAP (103 mg, 0.156 mmol), 3-aminomethyl-6-(3,3-dimethyl-butyl)-pyridine (150 mg, 0.78 mmol) and cesium carbonate (178 mg, 0.546 mmol) in degassed toluene (20 mL). Degas the mixture with vacuum/nitrogen purge and heat to 100 °C for 14 h. Cool the mixture to room temperature, dilute with EtOAc and filter through Celite®. Purify the crude mixture by chromatography on silica gel eluting with hexane and then hexane/EtOAc (19:1, 9:1 and 4:1) to obtain 7-chloro-6-[6-(3,3-dimethyl-butyl)-pyridin-3-yl-methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (149 mg, 82%). MS (ES+) *m/z*: 468 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[6-(3,3-dimethyl-butyl)-pyridin-3-yl-methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (140 mg, 0.29 mmol), to give the free base of the title compound as an oil (96 mg, 86%) that was used without further purification. MS (ES+) *m/z*: 372 $(M+H)^+$. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[6-(3,3-dimethyl-butyl)-pyridin-3-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (96 mg, 0.258 mmol) to give the title compound as a solid (119 mg, 94%). MS (ES+) *m/z*: 372 $(M+H)^+$.

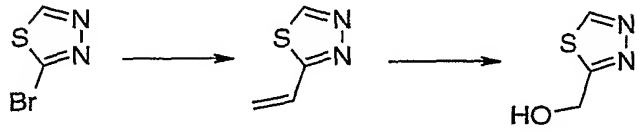
Examples 605-607

Examples 605-607 may be prepared essentially as described in Example 604 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
605		7-Chloro-6-(6-cyclohexylmethyl-pyridin-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	42	384 $(M+H)^+$
606		7-Chloro-6-[5-(3,3-dimethyl-butyl)-pyridin-2-yl-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	34	372 $(M+H)^+$
607		7-Chloro-6-[4-(1,3,3-trimethyl-butyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	47	385 $(M+H)^+$

Preparation 320

2-Hydroxymethyl-[1,3,4]-thiadiazole



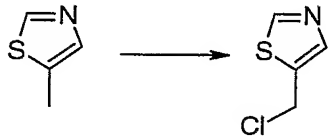
2-Vinyl-[1,3,4]-thiadiazole: Combine 2-bromo-[1,3,4]-thiadiazole (3.5 g, 21.2 mmol), tributylvinyltin (6.20 mL, 21.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (735 mg, 0.6 mmol) in anhydrous toluene (141 mL). Heat the mixture at reflux for 18 h. Add methanol and dichloromethane to dissolve the residue and evaporate onto silica gel.

Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 1:4 gradient) to give the desired intermediate (0.49 g, 21%). GC-MS *m/z*: 112 (M^+).

2-Hydroxymethyl-[1,3,4]-thiadiazole: At –10 °C bubble ozone through a solution of 2-vinyl-[1,3,4]-thiadiazole (400 mg, 3.57 mmol) in methanol (18 mL). After 20 min the starting material is consumed. Add then sodium borohydride (37 mg, 0.98 mmol) and warm to room temperature. Evaporate the mixture and purify the residue by passage through a pad of silica gel eluting with methanol/dichloromethane (98:2 to 96:4 gradient) to give the title compound (0.24 g, 60%). MS (ES+) *m/z*: 117 $(M+H)^+$.

Preparation 321

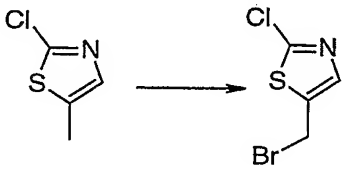
5-Chloromethylthiazole



Combine 5-methylthiazole (1.5 g, 15.1 mmol), *N*-chlorosuccinimide (2.6 g, 19.4 mmol) and AIBN (0.26 g, 1.6 mmol) in carbon tetrachloride (15 mL). Reflux under nitrogen for 3 h. Cool the reaction mixture and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give the title compound as a yellow oil (0.38 g, 19%).

Preparation 322

5-Bromomethyl-2-chlorothiazole

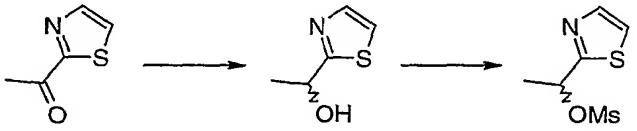


5-Chloromethyl-2-chlorothiazole: Combine 5-methyl-2-chlorothiazole (1.05 g, 7.5 mmol), NBS (1.7 g, 9.6 mmol) and AIBN (0.12 g, 0.73 mmol) in carbon tetrachloride (10 mL). Reflux under nitrogen for 7 h. Cool and concentrate *in vacuo*. Purify by

chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the title compound as a yellow oil (0.82 g, 51%).

Preparation 323

(±)-1-Methanesulfonyloxy-1-thiazol-2-yl-ethyl

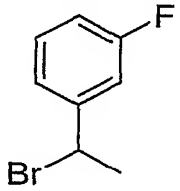


(±)-1-Thiazol-2-yl-ethanol: Add sodium borohydride (357 mg, 9.4 mmol) portionwise, over 5 min, to a solution of 2-acetylthiazole (1.0 g, 7.8 mmol) in methanol (25 mL) at 0 °C under a nitrogen atmosphere. Stir the mixture for 2 h at room temperature. Concentrate the mixture *in vacuo*, dilute the residue with brine (30 mL) and adjust the mixture to pH 6 with 5N aqueous HCl (10 mL). Extract the mixture with EtOAc (40 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate (1.0 g, 99%). GC-MS *m/z*: 129 (M^+).

(±)-1-Methanesulfonyloxy-1-thiazol-2-yl-ethyl: Dissolve 1-thiazol-2-yl-ethanol (1.0 g, 7.7 mmol) in dichloromethane (30 mL) and triethylamine (1.2 mL, 8.5 mmol). Cool the solution to 0°C, then add methanesulphony chloride (690 µl, 8.9 mmol) under a nitrogen atmosphere. Stir the solution for 1.5 h at room temperature, then wash with saturated aqueous $NaHCO_3$ (30 mL). Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with dichloromethane/hexane/methanol (50:45:5) to obtain the title compound (1.3 g, 81%). GC-MS *m/z*: 207 (M^+).

Preparation 324

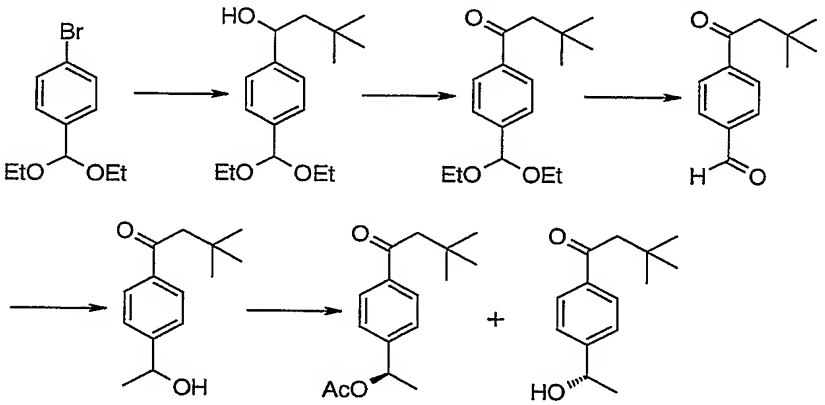
(±)-1-(3-Fluorophenyl)ethyl bromide



Dissolve (±)-1-(3-fluorophenyl)ethanol (250 mg, 1.786 mmol) in carbon tetrachloride (10 mL). Add phosphorus tribromide (0.1 mL, 1.786 mmol) at 0 °C and stir the solution at room temperature overnight. Dilute the reaction mixture with dichloromethane and wash with brine. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound (285 mg) that was used without any further purification.

Preparation 325

(*S*)-1-[4-(1-Hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one



1-[4-(Diethoxymethyl)-phenyl]-3,3-dimethylbutan-1-ol: Dissolve 1-bromo-4-(diethoxymethyl)-benzene (6.1 g, 23.55 mmol) in anhydrous THF (150 mL) and cool the solution to –78 °C. Add *n*-butyllithium (11.3 mL, 28.26 mmol, 2.5M solution in hexane) and stir the mixture for 30 min. Add 3,3-dimethylbutyraldehyde (4.7 mL, 35.33 mmol) and stir the mixture for 1 h. Add water and EtOAc. Warm the solution to room temperature and extract the aqueous layer three times with EtOAc. Dry the combined organic extracts with Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (93:7) to give the desired intermediate as a colorless oil (3.8 g, 58%).

1-[4-(Diethoxymethyl)-phenyl]-3,3-dimethylbutan-1-one: Dissolve 1-[4-(diethoxymethyl)-phenyl]-3,3-dimethylbutan-1-ol (3.8 g, 13.57 mmol) in hexane (50 mL). Add manganese dioxide (3.5 g, 40.71 mmol) and stir the mixture at 60 °C

overnight. Filter the solid and concentrate the filtrate *in vacuo* to give the desired intermediate as a colorless oil (3.49 g, 93%).

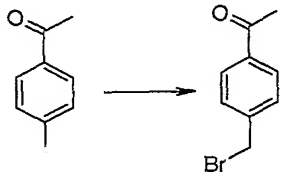
4-(3,3-Dimethyl-butyryl)-benzaldehyde: Dissolve 1-[4-(diethoxymethyl)-phenyl]-3,3-dimethylbutan-1-one (3.49 g, 12.55 mmol) in acetone (50 mL). Add *p*-toluenesulfonic acid monohydrate (238 mg, 1.256 mmol). Heat the mixture under reflux for 3 h. Concentrate *in vacuo* and partition the residue between water and EtOAc. Extract the aqueous phase three times with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (1.67 g, 65%).

1-[4-(1-Hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one: Dissolve 4-(3,3-dimethyl-butyryl)-benzaldehyde (1.67 g, 8.186 mmol) in anhydrous THF (20 mL) and cool the solution at –10 °C. Add methyl magnesium bromide (2.7 mL, 8.186 mmol, 3M solution in diethyl ether) and stir the mixture for 30 min. Add water at 0 °C, dilute with EtOAc and extract the aqueous layer three times with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter through a short pad of silica gel and concentrate *in vacuo* to give the desired intermediate as yellow oil (1.519 g, 84%).

(*S*)-1-[4-(1-hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one: Dissolve 1-[4-(1-hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one (1.519 g, 6.905 mmol) in diisopropyl ether (20 mL). Add 4Å molecular sieves powder (1.5 g), vinyl acetate (2 mL) and lipase Candida Antarctica acrylic resin (150 mg). Stir the mixture at room temperature overnight. Remove the solid residue by filtration. Concentrate the filtrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give (*R*)-1-(1-acetoxi-ethyl)-4-(3,3-dimethyl-butyryl)-benzene as colorless oil (0.661 g, 36%) and (*S*)-1-[4-(1-hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one as a light yellow oil (0.737 g, 49%).

Preparation 326

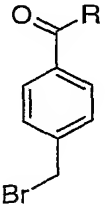
4-Acetyl-benzyl bromide



Heat a mixture of 4'-methylacetophenone (5 g, 37.26 mmol), NBS (6.964 g, 39.12 mmol), and AIBN (153 mg, 0.93 mmol) in carbon tetrachloride (120 mL) for 14 h at reflux. Cool to ambient temperature and wash sequentially with water (100 mL), 1M aqueous HCl (100 mL), 5% aqueous $NaHCO_3$ (100 mL) and brine (100 mL). Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (19:1, 9:1) to provide the title compound as oil (5.191 g, 65%). GC-MS *m/z*: 213 (M^+).

Preparations 353-354

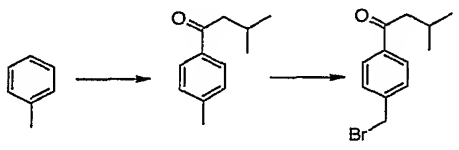
The compounds of Preparations 353-354 may be prepared essentially as described in Preparation 326 using 4'-methylpropiophenone (Preparation 353) and 4'-methylbutyrophenone (Preparation 354). Yields are shown in the Table below.



Prep.	R	Compound	Yield (%)
353	Et	4-Propionyl-benzyl bromide	92
354	*n*-Pr	4-Butyryl-benzyl bromide	42

Preparation 329

4-(3-Methyl-butyryl)-benzyl bromide

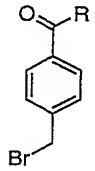


3,4'-Dimethylbutyrophenone: Add slowly isovaleryl chloride (3.0 g, 24.88 mmol) to an ice-cold stirred solution of aluminum trichloride (4.976 g, 37.32 mmol) in anhydrous toluene (60 mL). Stir the reaction mixture at ambient temperature overnight. Add slowly ice-cold water and extract the mixture twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (4.38 g, 100%) that was used without any further purification. GC-MS *m/z*: 176 (M^+).

4-(3-Methyl-butyryl)-benzyl bromide: Heat a mixture of 3,4'-dimethylbutyrophenone (3 g, 17.02 mmol), NBS (3.787 g, 16.18 mmol), and AIBN (70 mg, 0.425 mmol) in carbon tetrachloride (80 mL) for 14 h at reflux. Cool to ambient temperature and filter the mixture. Concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (9:1) to provide the title compound as oil (2.802 g, 65%). GC-MS *m/z*: 255 (M^+).

Preparations 356-357

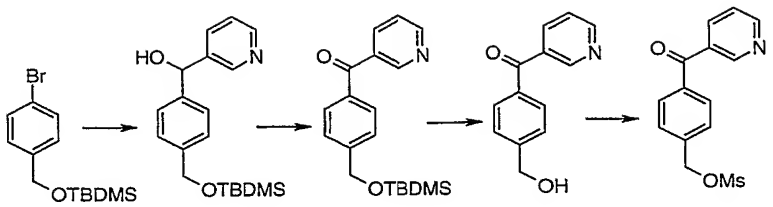
The compounds of Preparations 356-357 may be prepared essentially as described in Preparation 329 using the appropriate acyl chloride. Overall yields and GC-MS data are shown in the Table below.



Prep.	R	Compound	Yield (%)	GC-MS *m/z*
330	*i*-Propyl	4-Isobutyryl-benzyl bromide	32	241 $(M)^+$
357	2-Pyridyl	4-(Pyridine-2-carbonyl)-benzyl bromide	9	276 $(M)^+$

Preparation 332

4-(Pyridine-3-carbonyl)-benzyl methanesulfonate



[4-(*tert*-Butyldimethylsilyloxymethyl)-phenyl]-pyridin-3-yl-methanol: Dissolve 4-(*tert*-butyldimethylsilyloxymethyl)bromobenzene (1 g, 3.319 mmol, prepared by following the procedure described in *J. Am. Chem. Soc.* **1995**, *117*, 704-714) in anhydrous THF (20 mL). Cool the solution to –78 °C, add *n*-BuLi (4.149 mL, 6.638 mmol, 1.6M solution in hexane) and stir at this temperature for 1.5 h. Warm to –60°C, stir for an additional 30 min and add 3-pyridine carboxaldehyde. Allow the reaction mixture to warm gradually to room temperature and stir overnight. Add brine and extract with EtOAc. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and EtOAc to give the desired intermediate (380 mg, 35%). MS (ES+) *m/z*: 330 $(M+H)^+$.

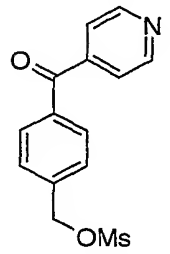
[4-(*tert*-Butyldimethylsilyloxymethyl)-phenyl]-pyridin-3-yl-methanone: Add manganese dioxide (1.44 g) to a stirred solution of [4-(*tert*-butyldimethylsilyloxymethyl)-phenyl]-pyridin-3-yl-methanol (360 mg, 0.303 mmol) in anhydrous 1,4-dioxane (25 mL). Heat the mixture to 70 °C overnight. Cool the reaction mixture to room temperature, filter through Celite® and wash with EtOAc. Concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (1:1) to provide the desired intermediate (233 mg, 65%). GC-MS *m/z*: 327 (M^+).

4-(Pyridine-3-carbonyl)-benzyl alcohol: Add tetrabutylammonium fluoride (1.37 mL, 1.37 mmol, 1M solution in THF) to a solution of [4-(*tert*-butyldimethylsilyloxymethyl)-phenyl]-pyridin-3-yl-methanone (225 mg, 0.687 mmol) in anhydrous THF (10 mL) at 0 °C and stir at this temperature for 1 h. Concentrate the solvent *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with EtOAc to provide the desired intermediate (85 mg, 58%). MS (ES+) *m/z*: 214 $(M+H)^+$.

4-(Pyridine-3-carbonyl)-benzyl methanesulfonate: Dissolve 4-(pyridine-3-carbonyl)-benzyl alcohol (85 mg, 0.399 mmol) in dichloromethane (5 mL). Cool to 0 °C and add triethylamine (0.056 mL, 0.438 mmol) and methanesulfonyl chloride (0.033 mL, 0.438 mmol). Allow the mixture to warm to room temperature and stir for 2 h. Dilute the reaction mixture with dichloromethane and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to provide the title compound as oil (115 mg, 100%). GC-MS *m/z*: 291 (M^+).

Preparation 333

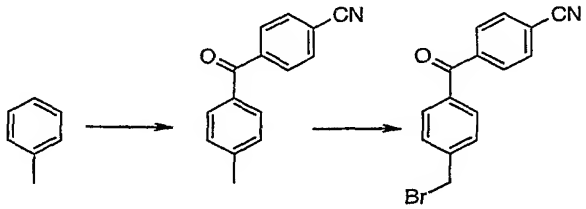
4-(Pyridine-4-carbonyl)-benzyl methanesulfonate



The compound of Preparation 333 may be prepared essentially as described in Preparation 332 using 4-(*tert*-butyldimethylsilyloxymethyl)bromobenzene and 4-pyridine carboxaldehyde (GC-MS *m/z* 291 $(M)^+$).

Preparation 334

4-(4-Cyano-benzoyl)-benzyl bromide



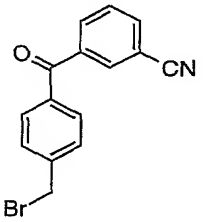
4-(4-Methyl-benzoyl)-benzonitrile: Suspend 4-cyanobenzoyl chloride (2.0 g, 12 mmol) in anhydrous toluene (30 mL). Add aluminum trichloride (2.4 g, 18 mmol) in three portions and stir the reaction mixture at ambient temperature overnight. Cool to 0°C, add carefully water and extract the mixture twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give a solid. Suspend the solid in

diethyl ether and filter to obtain the desired intermediate (1.30 g, 49%) that was used without any further purification. GC-MS *m/z*: 221 (M^+).

4-(4-Cyano-benzoyl)-benzyl bromide: Heat a mixture of 4-(4-methyl-benzoyl)-benzonitrile (300 mg, 1.356 mmol), NBS (386 mg, 2.169 mmol), and AIBN (22 mg, 0.136 mmol) in carbon tetrachloride (10 mL) for 14 h at reflux. Add additional NBS (121 mg) and AIBN (11 mg) and reflux the mixture for 3 h. Cool the reaction mixture to ambient temperature and filter the mixture. Concentrate the filtrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (9:1) to provide the title compound as a solid (286 mg, 70%). GC-MS *m/z*: 300 (M^+).

Preparation 335

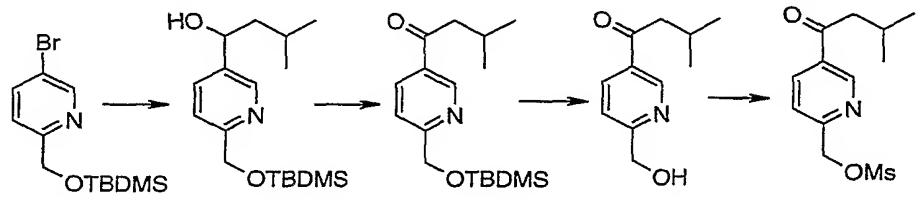
4-(3-Cyano-benzoyl)-benzyl bromide



The compound of Preparation 335 may be prepared essentially as described in Preparation 334 using 3-cyanobenzoyl chloride (GC-MS *m/z* 300 (M^+)).

Preparation 336

2-Methanesulfonyloxymethyl-5-(3-methyl-butyryl)-pyridine



2-(*tert*-Butyldimethylsilyloxymethyl)-5-(1-hydroxy-3-methyl-butyl)-pyridine: Dissolve 5-bromo-2-(*tert*-butyldimethylsilyloxymethyl)-pyridine (0.5 g, 1.654 mmol, prepared by following the procedure described in *J. Med. Chem.* **1987**, 30, 871-880) in anhydrous THF (12 mL). Cool the solution to –78 °C, add *n*-BuLi (1.14 mL, 1.819 mmol, 1.6M solution in hexane) and stir at this temperature for 40 min. Add slowly isovaleryl aldehyde (0.284 mL, 2.646 mmol) and stir the mixture for 5 h at –78 °C. Add additional isovaleryl aldehyde (0.089 mL, 0.827 mmol) and stir the mixture for 1.5 h at –78 °C. Add ammonium chloride at –78 °C and warm the mixture to room temperature. Add EtOAc and extract the aqueous layer twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (4:1) to give the desired intermediate as oil (330 mg, 64%). GC-MS *m/z*: 309 (M^+).

2-(*tert*-Butyldimethylsilyloxymethyl)-5-(3-methyl-butyryl)-pyridine: Add manganese dioxide (1.32 g) to a stirred solution of 2-(*tert*-butyldimethylsilyloxymethyl)-5-(1-hydroxy-3-methyl-butyl)-pyridine (330 mg, 1.066 mmol) in anhydrous 1,4-dioxane (30 mL). Heat the mixture to 70 °C overnight. Cool the reaction mixture to room temperature, filter through Celite® and wash with EtOAc. Concentrate the filtrate *in vacuo* to provide the desired intermediate as oil (327 mg, 100%). GC-MS *m/z*: 307 (M^+).

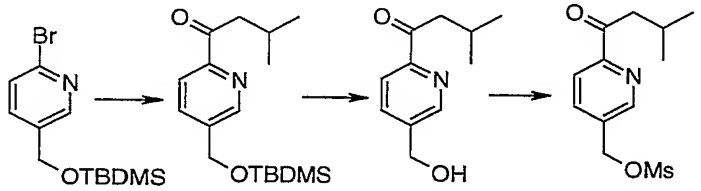
2-Hydroxymethyl-5-(3-methyl-butyryl)-pyridine: Add tetrabutylammonium fluoride (2.13 mL, 2.13 mmol, 1M solution in THF) to a solution of 2-(*tert*-butyldimethylsilyloxymethyl)-5-(3-methyl-butyryl)-pyridine (330 mg, 1.066 mmol) in anhydrous THF (20 mL) at 0 °C and stir at this temperature for 1 h. Concentrate the solvent *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with EtOAc to provide the desired intermediate (327 mg, 100%).

2-Methanesulfonyloxymethyl-5-(3-methyl-butyryl)-pyridine: Dissolve 2-hydroxymethyl-5-(3-methyl-butyryl)-pyridine (190 mg, 0.98 mmol) in dichloromethane (10 mL). Cool to 0 °C and add triethylamine (0.151 mL, 1.08 mmol) and methanesulfonyl chloride (0.083 mL, 1.08 mmol). Allow the mixture to warm to room

temperature and stir for 2 h. Dilute the reaction mixture with dichloromethane and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to provide the title compound as oil (263 mg, 98%).

Preparation 337

5-Methanesulfonyloxymethyl-2-(3-methyl-butyryl)-pyridine



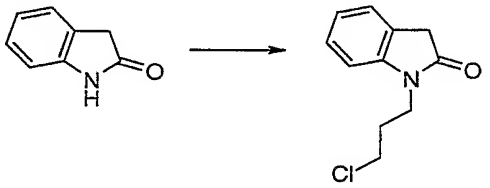
5-(*tert*-Butyldimethylsilyloxymethyl)-2-(3-methyl-butyryl)-pyridine: Dissolve 2-bromo-5-(tert-butyldimethylsilyloxymethyl)pyridine (1.99 g, 6.583 mmol, prepared by following the procedure described in *J. Org. Chem.* **2004**, *69*, 250-262) in anhydrous THF (20 mL). Cool the solution to –78 °C, add *n*-BuLi (4.32 mL, 6.912 mmol, 1.6M solution in hexane) and stir at this temperature for 40 min. Add slowly a solution of *N*-methoxy-*N*-methyl-3-methyl-butyramide (0.955 g, 6.583 mmol) in anhydrous THF (5 mL). Stir the mixture for 2 h at –78 °C and then allow the mixture to warm to room temperature. Add brine and extract the aqueous layer twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1) to give the desired intermediate as yellow oil (890 mg, 44%). GC-MS *m/z*: 307 (M^+).

5-Hydroxymethyl-2-(3-methyl-butyryl)-pyridine: Add tetrabutylammonium fluoride (5.853 mL, 5.853 mmol, 1M solution in THF) to a solution of 5-(*tert*-butyldimethylsilyloxymethyl)-2-(3-methyl-butyryl)-pyridine (900 mg, 2.927 mmol) in anhydrous THF (30 mL) at 0 °C and stir at this temperature for 2 h. Concentrate the solvent *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (3:2) to provide the desired intermediate (478 mg, 84%). MS (ES+) *m/z*: 194 $(M+H)^+$.

5-Methanesulfonyloxymethyl-2-(3-methyl-butyryl)-pyridine: Dissolve 5-hydroxymethyl-2-(3-methyl-butyryl)-pyridine (210 mg, 1.086 mmol) in dichloromethane (5 mL). Cool to 0 °C and add triethylamine (0.167 mL, 1.195 mmol) and methanesulfonyl chloride (0.093 mL, 1.195 mmol). Allow the mixture to warm to room temperature and stir for 2 h. Dilute the reaction mixture with dichloromethane and wash with saturated aqueous $NaHCO_3$. Dry the organic phase over Na_2SO_4, filter and concentrate *in vacuo* to provide the title compound (256 mg, 87%). GC-MS *m/z*: 271 (M^+).

Preparation 338

1-(3-Chloro-propyl)-1,3-dihydro-indol-2-one



Reflux together oxindole (2.66 g, 20.0 mmol), 1-bromo-3-chloropropane (2.56 mL, 26.0 mmol) and potassium carbonate (5.52 g, 40.0 mmol) in acetonitrile (300 mL) under nitrogen for 16 h. Cool the suspension to room temperature and filter off the precipitate. Concentrate the filtrate *in vacuo* and purify the crude mixture by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 3:2 gradient over 40 min) to give the title compound as an orange oil (1.65 g, 39%). MS (ES+) *m/z*: 210 $(M+H)^+$.

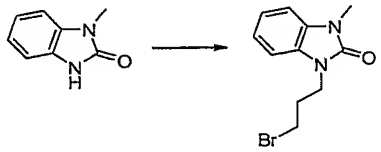
Preparation 339

1-(2-Chloro-ethyl)-pyrrolidin-2-one

Add thionyl chloride (5 mL) to 1-(2-hydroxy-ethyl)-pyrrolidin-2-one (1.12 mL, 10.0 mmol) dropwise then stir at room temperature for 10 min. Remove solvent *in vacuo* to give the title compound as an orange oil. MS (ES+) *m/z*: 148 $(M+H)^+$.

Preparation 340

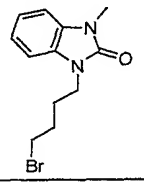
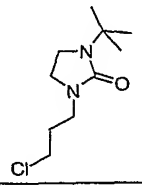
1-(3-Bromo-propyl)-3-methyl-1,3-dihydro-benzoimidazol-2-one



Add portion wise 3-methyl-1,3-dihydro-benzoimidazol-2-one (400 mg, 27.0 mmol) to a suspension of sodium hydride (1.296 g, 32.4 mmol of 60% dispersion in oil) in anhydrous THF (200 mL) under nitrogen over 15 min, then continue to stir for 30 min. Add 1,3-dibromopropane (11.0 mL, 108 mmol) and stir overnight. Then heat at reflux for 3 days. Cool the suspension to room temperature, pour into brine (400 mL), extract with diethyl ether (300 mL), dry over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40 min) to give the title compound as a colourless oil (2.15 g, 30%).

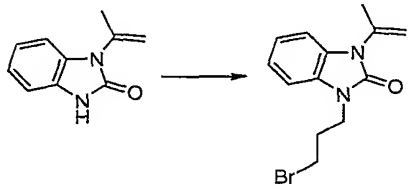
Preparations 341-342

The Compound of Preparation 341 may be prepared essentially as described in Preparation 340 using 3-methyl-1,3-dihydro-benzoimidazol-2-one and 1,4-dibromobutane. The compound of Preparation 342 may be prepared essentially as described in Preparation 340 using 1-*tert*-butyl-imidazolidin-2-one and 1-bromo-3-chloropropane. Yields are shown in the Table below.

Prep.	Structure	Compound	Yield (%)
341		1-(4-Bromo-butyl)-3-methyl-1,3-dihydro-benzoimidazol-2-one	56
342		1-*tert*-Butyl-(3-chloro-propyl)-imidazolidin-2-one	5

Preparation 343

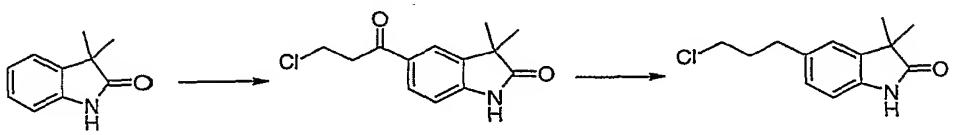
1-(3-Bromo-propyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one



Add sodium hydride (600 mg, 16.5 mmol of 60% dispersion in oil) to a solution of 1-isopropenyl-1,3-dihydro-benzoimidazol-2-one (1.311 g, 7.53 mmol) in anhydrous DMF (10 mL) under nitrogen at room temperature and stir for 2 h. Add 1-bromo-3-chloropropane (900 μL, 9.03 mmol) and stir for 3 days. Pour the suspension into water (100 mL), extract with diethyl ether (2 x 50 mL). Wash the organic extract with brine (100 mL), dry over $MgSO_4$ and concentrate *in vacuo* to give the title compound impurified with 1-(3-chloro-propyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one (2.03 g, 1:1 mixture). MS (ES+) *m/z*: 251 $(M+H)^+$, 293 $(M+H)^+$.

Preparation 344

5-(3-Chloropropyl)-3,3-dimethyl-1,3-dihydro-indol-2-one

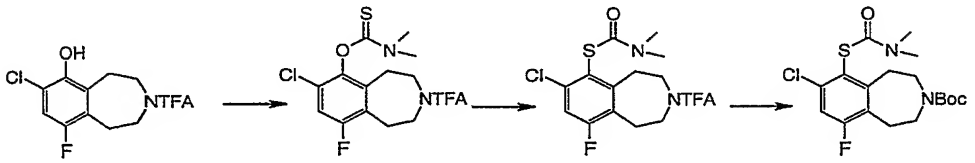


5-(3-Chloropropionyl)-3,3-dimethyl-1,3-dihydro-indol-2-one: Under nitrogen atmosphere, add chloropropionyl chloride (1.54 mL, 16.13 mmol) to a mixture of 3,3-dimethyl-1,3-dihydro-indol-2-one (2.0 g, 12.41 mmol) and aluminium trichloride (10.26 g, 76.92 mmol) in carbon disulphide (70 mL). Heat under reflux for 3 h then allow to cool. Decant off the solvent and replace it carefully with ice/water (200 mL). Allow the resultant suspension to stir for 20 min before filtering off the product and washing with water (80 mL). Dry *in vacuo* to obtain the desired intermediate as a pale brown solid (3.08 g, 99%).

5-(3-Chloropropyl)-3,3-dimethyl-1,3-dihydro-indol-2-one: Under nitrogen atmosphere, add 5-(3-chloropropyl)-3,3-dimethyl-1,3-dihydro-indol-2-one (3.08 g, 12.24 mmol) to trifluoroacetic acid (9.4 mL, 122.4 mmol). Cool the resulting suspension to 0 °C and then add triethylsilane (4.5 mL, 28.2 mmol) dropwise over 2 min. Heat at 45 °C for 30 min then stir at ambient temperature overnight. Pour the reaction mixture onto ice/water (100 mL) and extract with EtOAc (2 x 100 mL). Dry the combined extracts over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 4:1 gradient), to give the title compound as a yellow-orange solid (2.12 g, 73%).

Preparation 345

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Chloro-6-(*O*-dimethylthiocarbamoyl)-9-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat 7-chloro-9-fluoro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.56 g, 1.8 mmol) at reflux in anhydrous 1,4-dioxane (18 mL) with triethylamine (1.01 mL, 7.2 mmol), *N,N*-dimethyl-4-aminopyridine (22 mg, 0.18 mmol) and dimethylthiocarbamoyl chloride (0.67 g, 5.4

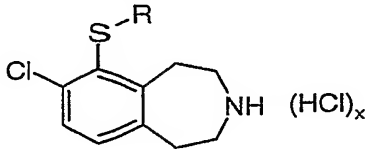
mmol) for 16 h. Cool and wash the mixture with 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 to 3:2 gradient) to give the desired intermediate as a yellow oil that solidifies on standing (0.69 g, 96%). MS (ES+) *m/z*: 399 $(M+H)^+$.

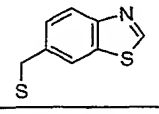
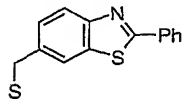
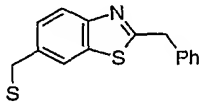
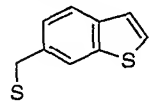
7-Chloro-6-dimethylcarbamoylthio-9-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat 7-chloro-6-(*O*-dimethylthiocarbamoyl)-9-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.69 g, 1.73 mmol) in diphenyl ether (6 mL) at 245 °C for 2.5 h. Cool the mixture and load onto a column of silica gel. Wash diphenyl ether off with hexane and elute with hexane/EtOAc (1:0 to 3:2 gradient) to give the desired intermediate (0.44 g, 64%). MS (ES+) *m/z*: 399 $(M+H)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat 7-chloro-6-dimethylcarbamoylthio-9-fluoro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.5 mmol) in methanol (50 mL) with potassium carbonate (0.28 g, 2 mmol) at reflux for 5 h. Cool the mixture, add dropwise a solution of di-*tert*-butyl-dicarbonate (0.22 g, 1.0 mmol) in dichloromethane (20 mL) and stir 17 h. Evaporate the mixture onto silica gel and purify by chromatography eluting with hexane/EtOAc (1:0 to 3:2 gradient) to give the title compound (0.12 g, 62%). MS (ES+) *m/z*: 303 $(M+H\text{-}Boc)^+$.

Examples 608-611

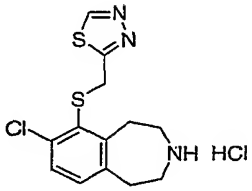
Examples 608-611 may be prepared essentially as described in Example 350 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted chloromethylheterocycle or bromomethylheterocycle. MS (ES+) data are shown in the Table below.



Ex.	SR	Compound	MS (ES+ or APCI+)
608		7-Chloro-6-(benzothiazol-6-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	361 $(M+H)^+$
609		7-Chloro-6-(2-phenyl-benzothiazol-6-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	437 $(M+H)^+$
610		7-Chloro-6-(2-benzyl-benzothiazol-6-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	451 $(M+H)^+$
611		7-Chloro-6-(benzothiophen-6-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	360 $(M+H)^+$

Example 612

7-Chloro-6-([1,3,4]thiadiazol-2-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Hydrochloride



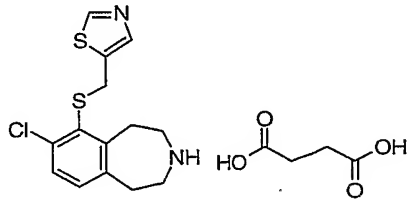
Stir 2-hydroxymethyl-[1,3,4]-thiadiazole (241 mg, 2.1 mmol) in thionylchloride (15 mL) for 1 h and concentrate *in vacuo*. Treat this residue with the thiolate prepared from 3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.4 g, 1.04 mmol) and potassium hydroxide (1.37 g, 24.5 mmol) in methanol (3.5 mL) according to General Procedure 7 to give 3-*tert*-butoxycarbonyl-7-chloro-6-([1,3,4]thiadiazol-2-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.3 g, 70%). Treat an aliquot with trifluoroacetic acid to obtain the mass spectrum. MS (ES+) *m/z*: 312 $(M+H)^+$.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-([1,3,4]thiadiazol-2-yl-methylthio)-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine (300 mg, 0.73 mmol). Use a method similar to the General Procedure 2-2 to give the title compound (208 mg, 82%). MS (ES+) *m/z*: 312 $(M+H)^+$.

Example 613

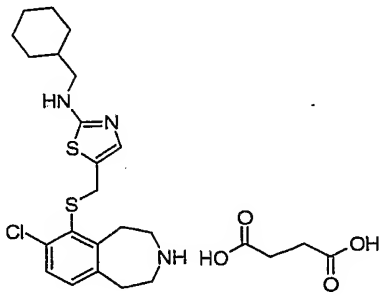
7-Chloro-6-(thiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to General Procedure 7, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-chloromethylthiazole to give, after deprotection and salt formation by methods similar to the General Procedures 1-5 and 2-1, the title compound as a white solid (700 mg, 80% overall). HRMS (ES+) *m/z*: 311.0427 $(M+H)^+$.

Example 614

7-Chloro-6-[2-(cyclohexylmethylamino)-thiazol-5-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

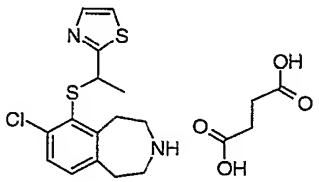


Use a method similar to General Procedure 7 using 3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-bromomethyl-2-chlorothiazole to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2-chlorothiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (0.9 g, 71%). Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(2-chlorothiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (120 mg, 0.27 mmol) and cyclohexylmethylamine (1 mL, 7.7 mmol) in

absolute ethanol (1 mL) in a heavy walled Pyrex tube. Heat the reaction in an oil bath at 82 °C for 24 h. Cool the reaction mixture and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1). Use methods similar to General Procedures 1-5 and 2-1 to deprotect and give the title compound as yellow oil (19 mg, 26% overall). MS (ES+) *m/z*: 422 $(M+H)^+$.

Example 615

(-)-7-Chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



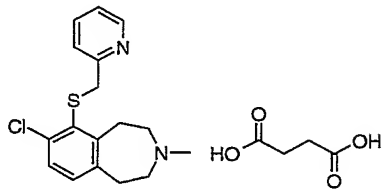
Add potassium hydroxide (3.9 g, 70 mmol) to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (900 mg, 2.3 mmol) in methanol (25 mL) under a nitrogen atmosphere. Heat the mixture at 80 °C for 1.5 h. Cool the mixture to ambient temperature, then concentrate *in vacuo* to an oil. Dissolve the oil in EtOAc (50mL) and wash with saturated aqueous ammonium chloride (30 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to an oil (735 mg). Dissolve the oil in anhydrous DMSO (20 mL), then add triethylamine (1.9 mL, 14 mmol) and (±)-1-methanesulfonyloxy-1-thiazol-2-yl-ethyl (1.3 g, 6.3 mmol) at ambient temperature under nitrogen. Heat the mixture at 40 °C for 1 h. Cool the reaction to room temperature, then dilute the mixture with hexane/EtOAc (1:1, 50 mL) and wash with aqueous 5% sodium chloride (3 x 50 mL). Separate the organic layer and back extract the aqueous layer with EtOAc (3 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 7:3 gradient) to obtain (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (779 mg, 79%). MS (ES+) *m/z*: 425.0 $(M+H)^+$.

Separate (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (770 mg, 1.8 mmol) by normal phase chiral chromatography [Chiralpak AD, 8 x 30 cm, eluting with heptane/3A ethanol (9:1)]. Collect the 2nd eluting isomer of 3-*tert*-butoxycarbonyl-7-chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine {348 mg, 99% ee [Chiralpak AD-H, 4.6 x 150 mm, eluant heptane/3A ethanol (9:1)]}.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[1-(thiazol-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine isomer 2. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (98:2 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (350 mg, 96%). MS (ES+) *m/z*: 325.0 $(M+H)^+$. $[\alpha]^{20}_D$ –160° (c 0.5, MeOH).

Example 616

7-Chloro-3-methyl-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine . Succinate



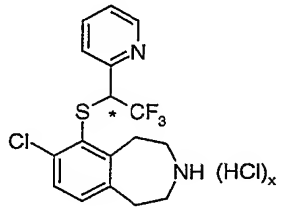
Suspend 7-chloro-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride in saturated aqueous $NaHCO_3$ and extract three times with EtOAc. Dry the combined organic extracts over $MgSO_4$. Filter and concentrate in *vacuo* to give the free base as a yellow oil. Combine the free base (0.2 g, 0.66 mmol), sodium triacetoxyborohydride (0.78 g, 3.7 mmol), formaldehyde (37% solution in water, 0.2 mL, 2.7 mmol), and acetic acid (0.45 mL, 7.9 mmol), in 1,2-dichloroethane (5 mL). Stir at room temperature for 12 h. Concentrate the crude reaction mixture *in vacuo* and partition the residue between EtOAc/water. Separate the layers and extract the aqueous phase with EtOAc (3 x 30 mL). Wash the combined organic extracts with 1M aqueous NaOH. Dry

over $MgSO_4$, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with 2M ammonia in methanol/dichloromethane (4:96).

Use a method similar to the General Procedure 2-1 to give the title compound as a sticky glass (140 mg, 48%). HRMS (ES+) *m/z*: 319.1029 $(M+H)^+$.

Examples 617 and 618

7-Chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride Isomer 1 and 7-Chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride Isomer 2



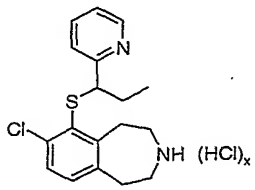
Separate the two enantiomers of (±)-7-chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride by normal phase chiral chromatography (Chiralpak AD, 2 x 25 cm, eluting with heptane/ethanol (85:15) with 0.2% DMEA).

Subject the first eluting isomer to the General Procedure 1-4 to obtain 7-chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride isomer 1 [99% ee (Chiralpak AD-H, 4.6 x 150 mm, eluting with heptane/ethanol (85:15) with 0.2% DMEA, flow rate 0.6 mL/min)]. MS (ES+) *m/z*: 373.1 $(M+H)^+$.

Subject the second eluting isomer to the General Procedure 1-4 to obtain 7-chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride isomer 2 [99% ee (Chiralpak AD-H, 4.6 x 150 mm, eluting with heptane/ethanol (85:15) with 0.2% DMEA, flow rate 0.6 mL/min)]. MS (ES+) *m/z* 373.1 $(M+H)^+$.

Example 619

(-)-7-Chloro-6-(1-pyridin-2-yl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

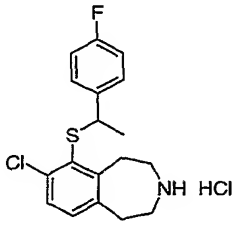


Separate the two enantiomers of (±)-7-chloro-6-(1-pyridin-2-yl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride by normal phase chiral chromatography (Chiralcel OJ, 8 x 33 cm, eluting with heptane/methanol/3A ethanol (85:10:5) with 0.2% DMEA).

Subject the second eluting isomer to the General Procedure 1-4 to obtain the title compound [93% ee (Chiralcel OJ, 4.6 x 250 mm, eluting with heptane/methanol/3A ethanol (90:5:5) with 0.2% DMEA, flow rate 0.6 mL/min)]. MS (ES+) *m/z*: 333.1 $(M+H)^+$. $[\alpha]^{20}_D$ –240.6° (c 0.5, MeOH).

Example 620

(±)-7-Chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



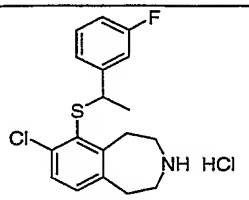
Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (415 mg, 1.08 mmol) in methanol (20 mL) and add potassium hydroxide (1.938 g, 34.53 mmol). Heat at 60 °C for 4 h. Cool the reaction mixture to ambient temperature, add aqueous saturated ammonium chloride and concentrate *in vacuo*. Partition the residue between EtOAc and water. Dry the organic phase over anhydrous Na_2SO_4 and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-

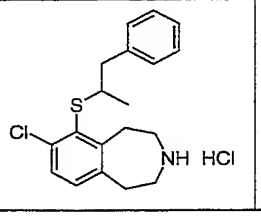
chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.34 g, 1.086 mmol). Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.34 g, 1.086 mmol) in anhydrous DMF (10 mL), add sodium hydride (65 mg, 1.63 mmol, 60% in mineral oil) and stir the mixture for 5 min. Add a solution of (±)-1-(4-fluorophenyl)ethyl bromide (332 mg, 1.63 mmol) in anhydrous DMF (5 mL) and heat the solution at 45 °C overnight. Cool to ambient temperature, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1 and 9:1) to give (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (397 mg, 84%). MS (ES+) *m/z*: 336 $(M+H\text{-Boc})^+$.

Use a method similar to the General Procedure 1-4 to deprotect (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (47 mg, 0.108 mmol) and give the title compound as a solid (39 mg, 99%). MS (ES+) *m/z*: 336 $(M+H)^+$.

Examples 621-622

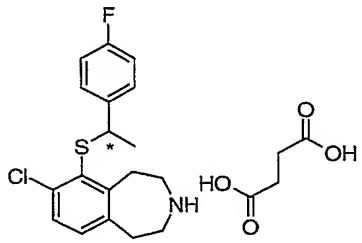
Examples 621-622 may be prepared essentially as described in Example 620 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alkyl bromide. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
621		(±)-7-Chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	75	336 $(M+H)^+$

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
622		(±)-7-Chloro-6-(1-methyl-2-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	80	332 $(M+H)^+$

Examples 623 and 624

7-Chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 1 and 7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 2



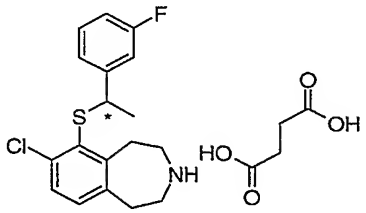
Separate the two enantiomers of (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral HPLC (Chiralcel OJ-H 4.6 x 150 mm column, eluting with methanol at 0.6 mL/min).

Subject Isomer 1 (t_R = 7.3 min, ee > 99.9%) to the General Procedure 2-1 to afford 7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate isomer 1 as a white solid. MS (ES+) *m/z* 336 $(M+H)^+$.

Subject Isomer 2 (t_R = 12.9 min, ee = 99.9%) to the General Procedure 2-1 to afford 7-chloro-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate isomer 2 as a white solid. MS (ES+) *m/z* 336 $(M+H)^+$.

Examples 625 and 626

7-Chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 1 and 7-chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 2



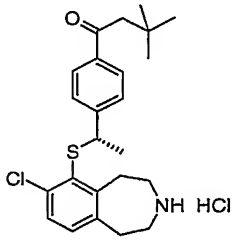
Separate the two enantiomers of (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral HPLC (Chiralcel OJ-H 4.6 x 150 mm column, eluting with methanol at 0.6 mL/min).

Subject Isomer 1 (t_R = 5.4 min, ee > 99.9%) to the General Procedure 2-1 to afford 7-chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate isomer 1 as a white solid. MS (ES+) *m/z* 336 $(M+H)^+$.

Subject Isomer 2 (t_R = 11.2 min, ee = 99.7%) to the General Procedure 2-1 to afford 7-chloro-6-[1-(3-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate isomer 2 as a white solid. MS (ES+) *m/z* 336 $(M+H)^+$.

Example 627

(S)-7-Chloro-6-{1-[4-(3,3-dimethylbutyryl)-phenyl]-ethylthio}-2,3,4,5-tetrahydro-1H-benzo[d]azepine Hydrochloride



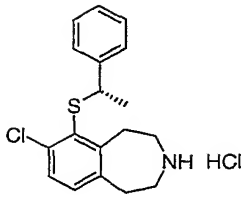
Heat the mixture of 3-tert-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1H-benzo[d]azepine (310 mg, 0.807 mmol) and potassium hydroxide

(1.45 g, 25.83 mmol) in methanol (5 mL) at 50 °C for 3 h. Cool the reaction mixture to room temperature and dilute with saturated aqueous NH_4Cl and EtOAc. Separate the layers and extract the aqueous layer three times with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate in vacuo. Dissolve the crude 3-tert-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1H-benzo[d]azepine in anhydrous DMF (2 mL) and cool at 0 °C. Add sodium hydride (21 mg, 0.888 mmol) and a solution of (R)-1-[4-(1-bromoethyl)-phenyl]-3,3-dimethylbutan-1-one {prepared by the mixture of (S)-1-[4-(1-hydroxyethyl)-phenyl]-3,3-dimethylbutan-1-one (213 mg, 0.969 mmol), triphenylphosphine (296 mg, 1.130 mmol) and NBS (201 mg, 1.13 mmol) in anhydrous THF (5 mL) at 0 °C and then room temperature}. Stir the mixture at 0 °C for 30 min and quench with water. Dilute with EtOAc and extract the aqueous layer three times with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate in vacuo. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (85:15) to give (S)-3-tert-butoxycarbonyl-7-chloro-6-{1-[4-(3,3-dimethylbutyryl)-phenyl]-ethylthio}-2,3,4,5-tetrahydro-1H-benzo[d]azepine as yellow oil (197 mg, 47%).

Use a method similar to the General Procedure 1-4, using (S)-3-tert-butoxycarbonyl-7-chloro-6-{1-[4-(3,3-dimethylbutyryl)-phenyl]-ethylthio}-2,3,4,5-tetrahydro-1H-benzo[d]azepine (197 mg, 0.382 mmol) to give the title compound as a white solid (161 mg, 93%). MS (ES+) m/z: 416 $(M+H)^+$; ee = 92%, t_R = 11.27 min (Chiralcel OJ, 4.6 x 250 mm, 45 °C , eluent: 20% isopropanol with 0.05% triethylamine in SFC, flow rate 2 mL/min, UV detector at 234 nm).

Example 628

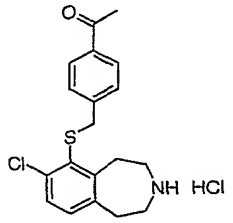
(*S*)-7-Chloro-6-(1-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Example 628 may be prepared essentially as described in Example 627 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (*R*)-(1-bromo-ethyl)-benzene (64% yield, MS (ES+) *m/z* 318 $(M+H)^+$).

Example 629

6-(4-Acetyl-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



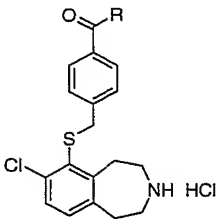
Use a method similar to the General Procedure 7 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.521 mmol) with 4-acetylbenzyl bromide (555 mg, 2.605 mmol). Purify the crude mixture by chromatography on silica gel eluting sequentially with hexane and hexane/EtOAc (9:1, 4:1) to obtain 6-(4-acetyl-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (190 mg, 82%).

Use a method similar to the General Procedure 1-4 to deprotect 6-(4-acetyl-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (170 mg, 0.381 mmol) and give the title compound as a white solid (140 mg, 96%). MS (ES+) *m/z*: 346 $(M+H)^+$.

Examples 630-634

Examples 630-634 may be prepared essentially as described in Example 629 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-

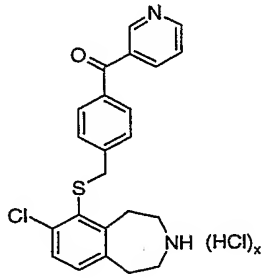
benzo[*d*]azepine and the appropriate benzyl bromide. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
630	Ethyl	7-Chloro-6-(4-propionyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	87	360 $(M+H)^+$
631	*n*-Propyl	6-(4-Butyryl-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	81	374 $(M+H)^+$
632	*i*-Propyl	7-Chloro-6-(4-isobutyryl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	69	374 $(M+H)^+$
633	*i*-Butyl	7-Chloro-6-[4-(3-methyl-butyryl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	68	388 $(M+H)^+$
634	2-Pyridyl	7-Chloro-6-[4-(pyridine-2-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	38	409 $(M+H)^+$

Example 635

7-Chloro-6-[4-(pyridine-3-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



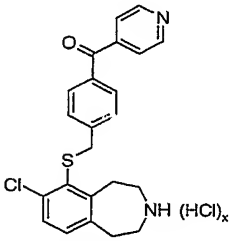
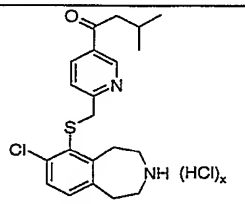
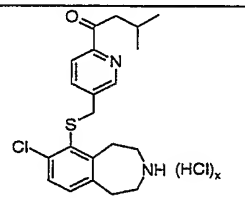
Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.39 mmol) in methanol (10 mL) and add

potassium hydroxide (0.7 g, 12.47 mmol). Heat at 60 °C for 4 h. Cool the reaction mixture to ambient temperature, add aqueous saturated ammonium chloride and concentrate *in vacuo*. Partition the residue between EtOAc and water. Dry the organic phase over anhydrous Na_2SO_4 and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.12 g). Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.12 g, 5.2 mmol) in anhydrous DMSO (6 mL) and add triethylamine (0.325 mL, 2.34 mmol) and 4-(pyridine-3-carbonyl)-benzyl methanesulfonate (114 mg, 0.39 mmol). Heat the solution at 40 °C overnight. Cool to ambient temperature, dilute the mixture with hexane/EtOAc (1:1, 100 mL), and wash the organic solution sequentially with brine and ice-cold water. Dry the organic layer over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (1:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(pyridine-3-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (123 mg, 64%).

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(pyridine-3-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (113 mg, 0.22 mmol) and give the title compound as a solid (105 mg, 99%). MS (ES+) *m/z*: 409 $(M+H)^+$.

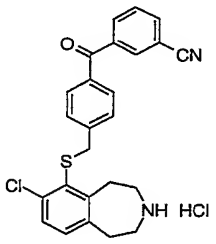
Examples 636-638

Examples 636-638 may be prepared essentially as described in Example 635 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate methanesulfonate. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
636		7-Chloro-6-[4-(pyridine-4-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	39	409 $(M+H)^+$
637		7-Chloro-6-[5-(3-methyl-butyryl)-pyridin-2-yl-methylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	69	389 $(M+H)^+$
638		7-Chloro-6-[6-(3-methyl-butyryl)-pyridin-3-yl-methylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	57	389 $(M+H)^+$

Example 639

7-Chloro-6-[4-(3-cyanobenzoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



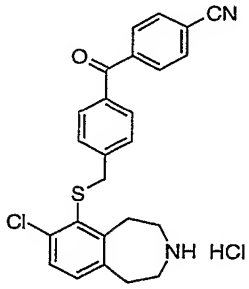
Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (12 mL) and add potassium hydroxide (0.935 g, 16.66 mmol). Heat at 60 °C for 4 h. Cool the reaction mixture to ambient temperature, add aqueous saturated ammonium chloride and concentrate *in vacuo*. Partition the residue between EtOAc and water. Dry the organic phase over anhydrous Na_2SO_4 and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.16 g, 5.2 mmol). Dissolve

the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.16 g, 0.52 mmol) in anhydrous DMSO (5 mL) and add triethylamine (0.435 mL, 3.12 mmol) and 4-(3-cyano-benzoyl)benzyl bromide (289 mg, 0.96 mmol). Heat the solution at 40 °C overnight. Cool to ambient temperature, dilute the mixture with hexane/EtOAc (1:1, 100 mL), and wash the organic solution sequentially with brine and ice-cold water. Dry the organic layer over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (9:1, 4:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3-cyanobenzoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (212 mg, 77%).

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3-cyanobenzoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.37 mmol) and give the title compound as a solid (136 mg, 77%). MS (ES+) *m/z*: 433 $(M+H)^+$.

Example 640

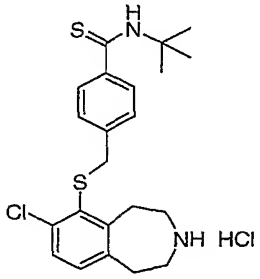
7-Chloro-6-[4-(4-cyanobenzoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Example 640 may be prepared essentially as described in Example 639 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(4-cyano-benzoyl)benzyl bromide (49% yield, MS (ES+) *m/z* 433 $(M+H)^+$).

Example 641

7-Chloro-6-(4-*tert*-butylthiocarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

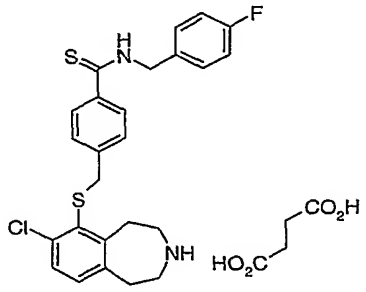


Combine 7-chloro-6-(4-*tert*-butylcarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine (53 mg, 0.13 mmol) with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (53 mg, 0.13 mmol) in anhydrous 1,4-dioxane (1 mL) in a sealed tube and heat at 100 °C for 2 h. Cool the reaction mixture to room temperature, concentrate *in vacuo* and purify the residue by SCX chromatography to obtain 7-chloro-6-(4-*tert*-butylthiocarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil. Purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2 x 250 mm, 5 micron, 22 mL/min of 0.1% aqueous HCl /acetonitrile (9:1 to 1:9) over 30 min, detector at 230 nm].

Use a method similar to the General Procedure 2-2 to obtain the title compound as a yellow solid (36 mg, 58%). MS (ES+) *m/z*: 419 $(M+H)^+$.

Example 642

7-Chloro-6-[4-(4-fluorobenzylthiocarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

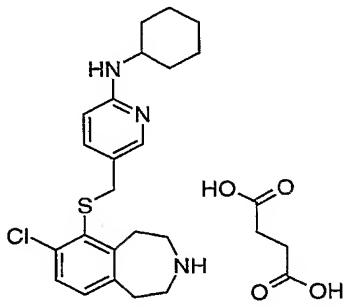


Combine 7-chloro-6-[4-(4-fluorobenzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (23 mg, 0.05 mmol) with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (23 mg, 0.05 mmol) in anhydrous 1,4-dioxane (1 mL) in a sealed tube and heat at 100 °C for 2 h. Cool the reaction mixture to room temperature, concentrate *in vacuo* and purify the residue by SCX chromatography to obtain 7-chloro-6-[4-(4-fluorobenzylthiocarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil.

Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (10 mg, 42%). MS (ES+) *m/z*: 471 $(M+H)^+$.

Example 643

7-Chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to General Procedure 7, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2 g, 5.2 mmol) and 2-chloro-5-(chloromethyl)pyridine (843 mg, 5.2 mmol) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.2 g, 95%). MS (ES+) *m/z*: 439.1 $(M+H)^+$.

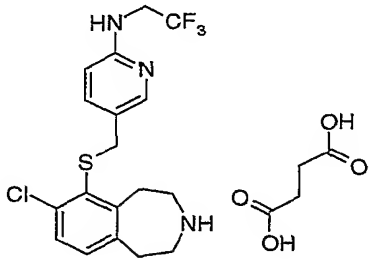
Slurry palladium(II) acetate (434 mg, 1.9 mmol), BINAP (1.2 g, 1.9 mmol), sodium-*tert*-butoxide (644 mg, 6.7 mmol), cyclohexylamine (1.4 g, 14.4 mmol) and 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.1 g, 4.8 mmol) in anhydrous toluene (70 mL). Degas the slurry under

house vacuum, then buble nitrogen. Heat the mixture to 95 °C for 16 h under a nitrogen atmosphere. Cool the mixture to room temperature, dilute with EtOAc (50 mL) and filter through Celite®. Concentrate the filtrate to an oil and purify by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 13:7 gradient) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (800 mg, 33%). MS (ES+) *m/z*: 502.2 $(M+H)^+$.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(6-cyclohexylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (790 mg, 1.6 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 95:5 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (670 mg, 82%). MS (ES+) *m/z*: 402.1 $(M+H)^+$.

Example 644

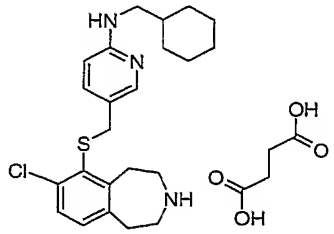
7-Chloro-6-(6-trifluoroethylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Example 644 may be prepared essentially as described in Example 643 by using 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,2,2-trifluoroethylamine (10% yield, MS (ES+) *m/z* 502.2 $(M+H)^+$).

Example 645

7-Chloro-6-(6-cyclohexylmethylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

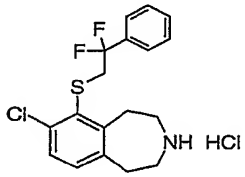


Add cyclohexylmethylamine (3 mL) to a flask containing 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (340 mg, 0.8 mmol) and ammonium chloride (50 mg, 0.92 mmol). Heat the contents in a sealed flask at 170 °C for 7 h. Cool the flask to room temperature, dilute with EtOAc (50 mL) and wash with water (20 mL). Collect the organic layer and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 4:1 gradient) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(6-cyclohexylmethylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (160 mg, 40%).

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(6-cyclohexylmethylamino-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1, 98:2, 96:4 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (115 mg, 70%). MS (ES+) *m/z*: 416.0 $(M+H)^+$.

Example 646

7-Chloro-6-(2,2-difluoro-2-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

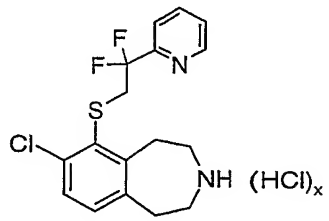


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (10 mL) and add potassium hydroxide (0.934 g, 16.64 mmol). Heat at 60 °C for 4 h. Cool the reaction mixture to ambient temperature, add aqueous saturated ammonium chloride and concentrate *in vacuo*. Partition the residue between EtOAc and water. Dry the organic phase over anhydrous Na_2SO_4 and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.163 g). Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.163 g, 0.52 mmol) in anhydrous DMSO (5 mL) and add triethylamine (0.43 mL, 3.12 mmol) and 2,2-difluoro-2-phenylethyl trifluoromethanesulfonate (151 mg, 0.52 mmol). Heat the solution at 40 °C overnight. Cool to ambient temperature, add water and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane and hexane/EtOAc (19:1, 9:1 and 4:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2,2-difluoro-2-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil (132 mg, 56%).

Use a method similar to the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(2,2-difluoro-2-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (132 mg, 0.29 mmol) and give the title compound as a solid (111 mg, 98%). MS (ES+) *m/z*: 354 $(M+H)^+$.

Example 647

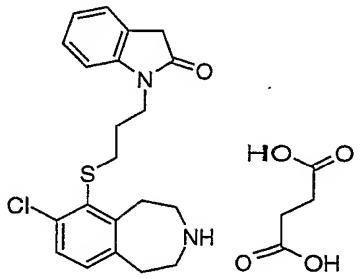
7-Chloro-6-(2,2-difluoro-2-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Example 647 may be prepared essentially as described in Example 646 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,2-difluoro-2-pyridin-2-yl-ethyl trifluoromethanesulfonate (prepared by following the procedure described in *J. Med. Chem.* **2003**, *46*, 461-473) (66% yield, MS (ES+) *m/z* 355 $(M+H)^+$).

Example 648

7-Chloro-6-[3-(2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



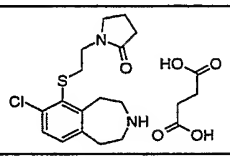
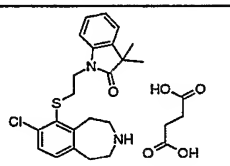
Add potassium hydroxide (899 mg, 16.64 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (10 mL). Heat the raction to 50 °C under nitrogen for 24 h, then cool to room temperature and add 1-(3-chloro-propyl)-1,3-dihydro-indol-2-one (217 mg, 1.04 mmol). Stir the reaction at room temperature for 4 days. Remove solvents *in vacuo*, add dichloromethane (20 mL) and water (20 mL). Remove the organic layer and dry using an ISCO® phase separator then concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(2-oxo-2,3-dihydro-indol-1-yl)-

propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as orange powder. MS (ES+) *m/z*: 509 $(M+Na)^+$.

Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.52 mmol) in dichloromethane (10 mL), then add TFA (2 mL) dropwise and stir for 2 h. Remove solvents in vacuo, then free base using an SCX column, eluting with 7M ammonia in methanol. Purify using UV-guided reverse phase HPLC [Supelco Discovery C18 column (21.2 x 100 mm, 5μm packing), 20 mL/min flow rate, eluting with water/acetonitrile/acetic acid gradient over 15 min, fraction collection triggered using UV detector (220 and 254 nm)] followed by SCX column, eluting with 7M ammonia in methanol, then Mass-guided reverse phase HPLC [Supelco Discovery C18 column (21.2 x 100 mm, 5μm packing), 25 mL/min flow rate, eluting with water/acetonitrile/acetic acid gradient over 12 min, fraction collection triggered by Electrospray MS] and SCX column. Concentrate *in vacuo*, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a light pink solid (51 mg, 19%). MS (ES+) *m/z*: 387 $(M+H)^+$.

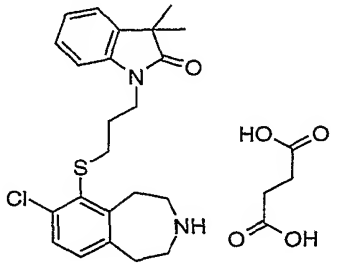
Examples 649-650

Examples 649-650 may be prepared essentially as described in Example 648 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted alkyl chloride. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
649		7-Chloro-6-[2-(2-oxo-pyrrolidin-1-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	71	325 $(M+H)^+$
650		7-Chloro-6-[2-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	32	401 $(M+H)^+$

Example 651

7-Chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



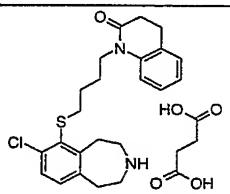
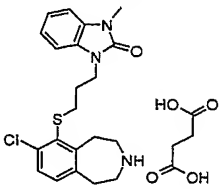
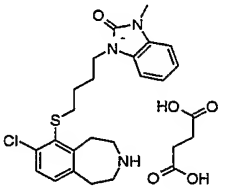
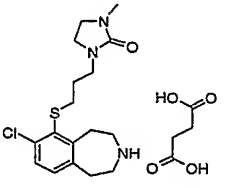
Add potassium hydroxide (170 mg, 3.03 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (187 mg, 0.49 mmol) in methanol (10 mL). Heat the reaction at reflux under nitrogen overnight. Then add further portion of KOH (867 mg, 15.45 mmol) and heat at reflux for 3 h. Then cool to room temperature and add 1-(3-bromo-propyl)-1,3-dihydro-3,3-dimethyl-indol-2-one (274 mg, 0.97 mmol, prepared by following the procedure described in *Perkin 1* **2000**, 769-774). Stir the reaction at room temperature overnight. Remove solvents *in vacuo*, add water and extract with diethyl ether (2 x 50 mL). Combine the organic extracts, wash with water (2 x 50 mL) and brine (50 mL). Dry over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with isohexane/EtOAc (1:0 to 1:1 gradient over 40 min) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colourless oil (330 mg), 50% contaminated with 1-(3-methoxypropyl)-1,3-dihydro-3,3-dimethyl-indol-2-one. MS (ES+) *m/z*: 537 $(M+Na)^+$.

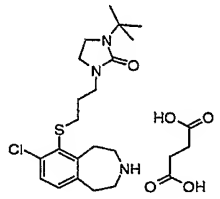
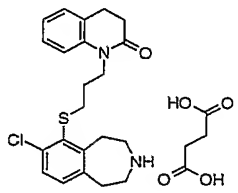
Dissolve 3-tert-butoxycarbonyl-7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-indol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (240 mg, 0.52 mmol) in dichloromethane (10 mL), then add TFA (1 mL) dropwise and stir at room temperature overnight. Remove solvents in vacuo to give a straw coloured oil (580 mg), then free base using an SCX column, eluting with 7M ammonia in methanol. Concentrate in

vacuo, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a solid (196 mg, 82%). MS (ES+) m/z: 415 $(M+H)^+$.

Examples 652-654

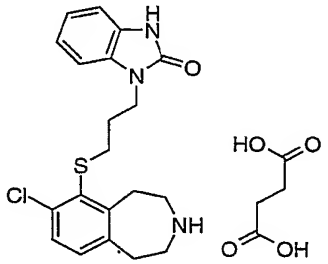
Examples 652-654 may be prepared essentially as described in Example 651 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate alkyl bromide. Examples 655-657 may be prepared essentially as described in Example 651 using the appropriate alkyl chloride. Overall yields and MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	Yield (%)	MS (ES+) *m/z*
652		7-Chloro-6-[4-(2-oxo-3,4-dihydro-2*H*-quinolin-1-yl)-butylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	71	414 $(M+H)^+$
653		7-Chloro-6-[3-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	31	402 $(M+H)^+$
654		7-Chloro-6-[4-(3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-butylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	31	416 $(M+H)^+$
655		7-Chloro-6-[3-(3-methyl-2-oxo-imidazolidin-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	29	354 $(M+H)^+$

656		7-Chloro-6-[3-(3-*tert*-butyl-2-oxo-imidazolidin-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	31	396 $(M+H)^+$
657		7-Chloro-6-[3-(2-oxo-3,4-dihydro-2*H*-quinolin-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	66	400 $(M+H)^+$

Example 658

7-Chloro-6-[3-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



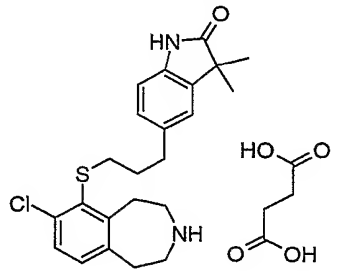
Add potassium hydroxide (933 mg, 16.6 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (10 mL). Heat the reaction at reflux under nitrogen 4 h. Then cool to room temperature and add 1-(3-bromo-propyl)-3-isopropenyl-1,3-dihydro-benzoimidazol-2-one (142 mg, 0.52 mmol). Stir the reaction at room temperature overnight. Remove solvents *in vacuo*, extract into diethyl ether (2 x 50 mL), wash with water (2 x 50 mL) and brine (50 mL). Dry over $MgSO_4$, filtrate and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (209 mg, 76%). MS (ES+) *m/z*: 550 $(M+Na)^+$.

Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (209 mg, 0.396 mmol) in

dichloromethane (10 mL), then add TFA (0.5 mL) dropwise and stir at room temperature overnight. Remove solvents *in vacuo* then free base using an SCX column, eluting with 7M ammonia in methanol. Concentrate *in vacuo*, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a solid (140 mg, 70%). MS (ES+) *m/z*: 388 $(M+H)^+$.

Example 659

7-Chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



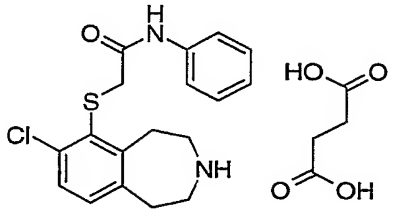
Under nitrogen atmosphere, add potassium hydroxide (138 mg, 2.46 mmol) to a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (375 mg, 0.97 mmol) in methanol (10 mL). Heat under reflux for 2 h then add further potassium hydroxide (159 mg, 2.83 mmol) and continue heating under reflux for another 6 h. Cool the reaction mixture and add dropwise *via* cannula a solution of 5-(3-chloropropyl)-3,3-dimethyl-1,3-dihydro-indol-2-one (245 mg, 1.03 mmol) in methanol (10 mL). Stir at ambient temperature overnight then heat at 50 °C for 5 h. Add potassium iodide (186 mg, 1.12 mmol) to the reaction mixture and then heat under reflux for 5 h. Concentrate *in vacuo* and partition the residue between water (100 mL) and EtOAc (50 mL). Extract the aqueous phase with EtOAc (2 x 50 mL). Wash the combined extracts with brine (50 mL), dry over $MgSO_4$, filter and concentrate *in vacuo* to obtain the crude mixture as a yellow oil. Dilute this oil with dichloromethane then re-concentrate *in vacuo* and repeat until a solid remains. Dry the solid in a vacuum oven to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow solid (481 mg) that was used without further purification. MS (ES+) *m/z*: 537 $(M+Na)^+$.

Add trifluoroacetic acid (0.2 mL, 2.6 mmol) to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (257 mg, 0.5 mmol) in dichloromethane (5 mL) then stir at ambient temperature over the weekend. Concentrate *in vacuo*. Dissolve the residue in methanol and load onto an SCX column. Elute with methanol followed by 7M ammonia in methanol. Collect the basic fraction and concentrate *in vacuo*. Purify the residue by prep-LCMS [Supelco Discovery C18 column (21.2 x 100 mm, 5μm packing), 25 mL/min flow rate, eluting with a water/acetonitrile gradient containing acetic acid as modifier over 12 min, fraction collection triggered by Electrospray MS] to give 7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid (101 mg, 25% over 2 steps). MS (ES+) *m/z*: 415 $(M+H)^+$.

Dissolve 7-chloro-6-[3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (101 mg, 0.24 mmol) in a mixture of diethyl ether (3 mL) and methanol (2 mL). Add succinic acid (28.7 mg, 0.24 mmol) and allow the resultant suspension to stir at ambient temperature for 2 h. Concentrate *in vacuo* and dry the residue in a vacuum oven to afford the title compound as a white solid. MS (ES+) *m/z*: 415 $(M+H)^+$.

Example 660

7-Chloro-6-(*N*-phenylcarbamoyl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



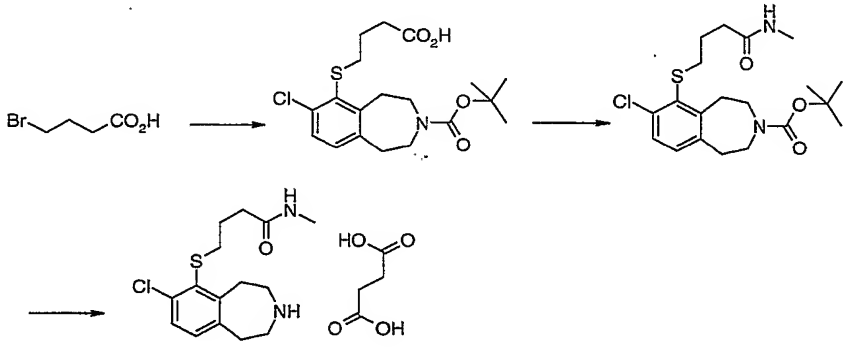
Add potassium hydroxide (890 mg, 15 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (180 mg, 0.47 mmol) in methanol (10 mL). Heat the reaction at reflux

under nitrogen 3 h. Then cool to room temperature, add 2-chloro-*N*-phenyl-acetamide (79 mg, 0.47 mmol) and stir overnight. Remove solvents *in vacuo*, extract into diethyl ether (2 x 50 mL), wash with water (2 x 50 mL) and brine (50 mL). Dry over $MgSO_4$, filtrate and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-(*N*-phenylcarbamoyl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (210 mg, 100%). MS (ES+) *m/z*: 460 $(M+Na)^+$.

Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(*N*-phenylcarbamoyl-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine(210 mg, 0.47 mmol) in dichloromethane (10 mL) then add TFA (0.5 mL) dropwise and stir at room temperature for 3 days. Remove solvents *in vacuo* then free base using an SCX column, eluting with 7M ammonia in methanol. Concentrate *in vacuo*, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a solid (150 mg, 69%). MS (ES+) *m/z*: 347 $(M+H)^+$.

Example 661

7-Chloro-6-(3-methylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



3-*tert*-Butoxycarbonyl-7-chloro-6-(3-carboxy-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add potassium hydroxide (700 mg, 12.5 mmol) in one portion to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.39 mmol) in methanol (10 mL). Heat the reaction at reflux under nitrogen 4 h. Then cool to room temperature, add 4-bromo-butyric acid (65 mg, 0.39 mmol) and stir for 3 days. Remove solvents *in vacuo*, neutralize with

ammonium chloride (200 mL) and extract into EtOAc (2 x 50 mL). Dry over $MgSO_4$, filtrate and concentrate *in vacuo* to give a clear oil (125 mg). Dissolve the oil in anhydrous DMF (10 mL) and add sodium hydride (30 mg, 0.78 mmol of 60% dispersion in oil) under nitrogen. Stir for 30 min. Add 4-bromo-butyric acid (65 mg, 0.39 mmol) and stir for 30 min. Pour into water (50 mL) and extract with diethyl ether (2 x 50 mL). Wash the combined organic extracts with brine (50 mL) and dry over $MgSO_4$. Concentrate the filtrate *in vacuo* to give the desired intermediate as a solid (146 mg, 94%). MS (ES+) *m/z*: 398 $(M+H)^+$.

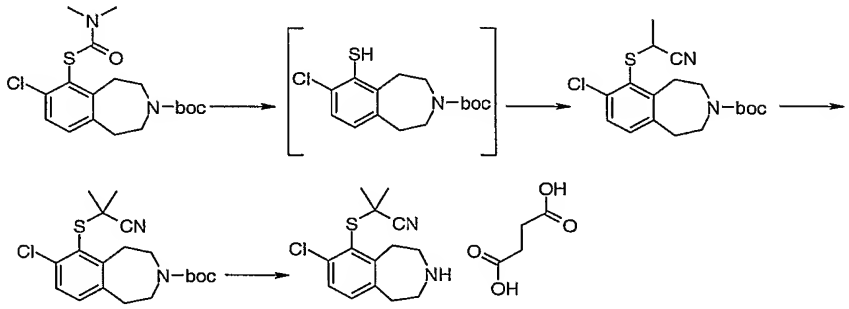
3-*tert*-Butoxycarbonyl-7-chloro-6-(3-methylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (123 mg, 0383 mmol) portion wise to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(3-carboxy-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (146 mg, 0365 mmol) and methylamine (182 µL, 0.365 mmol) in anhydrous DMF (5 mL) under nitrogen at 0 °C. Stir for 15 min then add diisopropylethylamine (127 µL, 0.73 mmol) in anhydrous DMF (1 mL) and continue to stir at 0 °C for 1 h. Warm to room temperature and continue to stir overnight. Pour into water (50 mL) and extract with EtOAc (3 x 20 mL). Wash the combined organic extracts with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). Dry over $MgSO_4$, filtrate and concentrate *in vacuo* to give a pale yellow oil (74 mg). MS (ES+) *m/z*: 398 $(M+H)^+$. Purify using Mass-guided reverse phase HPLC [Supelco Discovery C18 column (21.2 x 100 mm, 5µm packing), 25 mL/min flow rate, eluting with water/acetonitrile/acetic acid gradient over 12 min, fraction collection triggered by Electrospray MS]. Concentrate *in vacuo* to give the desired intermediate as a colourless oil (30 mg, 20%). MS (ES+) *m/z*: 435 $(M+Na)^+$.

7-Chloro-6-(3-methylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate: Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (30 mg, 0.07 mmol) in dichloromethane (10 mL) then add TFA (0.5 mL) dropwise and stir at room temperature for 3 days. Remove solvents *in vacuo* then free base using an SCX column, eluting with 7M ammonia in

methanol. Concentrate *in vacuo*, then use a method similar to the General Procedure 2-1 and freeze dry to give the title compound as a solid (21 mg, 72%). MS (ES+) *m/z*: 313 $(M+H)^+$.

Example 662

7-Chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



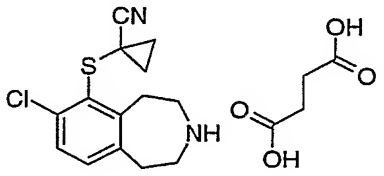
3-*tert*-Butoxycarbonyl-7-chloro-6-(1-cyano-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add potassium hydroxide (10.8 g , 192 mmol) to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3 g, 7.8 mmol) in degassed methanol (150 mL) under a nitrogen atmosphere. Heat the mixture at 80 °C for 6 h. Cool the mixture to ambient temperature, then concentrate *in vacuo* to an oil. Dissolve the oil in EtOAc (50mL), wash with aqueous saturated ammonium chloride (30 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to an oil (2.4 g). Dissolve the oil in anhydrous DMF (50 mL). Slowly add sodium hydride (470 mg, 11.7 mmol) portionwise over 5 min followed by 2-bromopropionitrile (1 mL, 11.7 mmol). Stir the mixture under nitrogen at ambient temperature for 16 h. Dilute the mixture slowly with EtOAc (100 mL) and wash with cold aqueous saturated ammonium chloride (50 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 3:1 gradient) to obtain the desired intermediate (2.5 g, 89%). MS (ES+) *m/z*: 267.2 $(M\text{-}Boc)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Slowly add a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.5 g, 6.8 mmol) in anhydrous THF (20 mL) to a slurry of sodium hydride (1.4 g, 34 mmol) in anhydrous THF (50 mL) at 0 °C under a nitrogen atmosphere. Stir the slurry for 5 min, then add iodomethane (12.7 mL, 204 mmol) to the slurry while maintaining the temperature below 30 °C. Stir the mixture for 3 h at ambient temperature then quench with methanol (10 mL) and concentrate *in vacuo*. Purify the crude mixture by chromatography on silica gel eluting with hexane/EtOAc (19:1 to 9:1 gradient) to obtain the desired intermediate (2 g, 79%). MS (ES+) *m/z*: 281.2 $(M+H\text{-Boc})^+$.

7-Chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate: Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.4 g, 3.5 mmol). Purify by chromatography on silica gel eluting with dichloromethane/2M ammonia in methanol (99:1 to 90:10 gradient) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (992 mg, 71%). MS (ES+) *m/z*: 281.2 $(M+H)^+$..

Example 663

7-Chloro-6-(1-cyano-cyclopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Add potassium hydroxide (5.4 g, 96.2 mmol) to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.5 g, 4.7 mmol) in degassed methanol (75 mL) under a nitrogen atmosphere. Heat the mixture at 80 °C for 6 h. Cool the mixture to ambient temperature,

then concentrate *in vacuo* to an oil. Dissolve the oil in EtOAc (50mL) and wash with saturated aqueous ammonium chloride (30 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to an oil (1.4 g). Dissolve the oil in anhydrous DMF (25 mL), then slowly add sodium hydride (282 mg, 7.1 mmol) and bromoacetonitrile (470 µl, 7.1 mmol). Stir the mixture under nitrogen at ambient temperature for 16 h. Dilute the mixture slowly with EtOAc (100 mL) and wash with cold aqueous saturated ammonium chloride (40 mL). Separate the organic layer and extract the aqueous layer with EtOAc (3 x 50 mL). Combine the organic extracts and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 7:3 gradient) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.34 g, 81%). MS (ES+) *m/z*: 253.2 $(M\text{-}Boc)^+$.

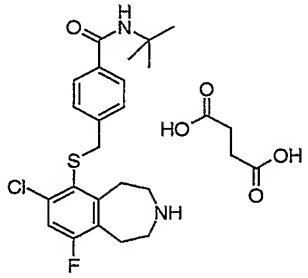
Add sodium bis(trimethylsilyl)amide (5.4 mL, 5.4 mmol, 1M solution in THF) at room temperature under nitrogen to a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-methylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (380 mg, 1.1 mmol) in anhydrous toluene (4 mL). Stir the solution for 10 min, then add quickly 1,2-dibromoethane (2.8 mL, 32.4 mmol) followed by anhydrous DMF (4 mL). An exothermic reaction was observed and the reaction temperature increased to 38 °C. Stir the mixture for 15 min at ambient temperature, then quench with methanol (2 mL). Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-cyclopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (259 mg).

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-cyclopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by reverse phase chromatography [Column: Symmetry C18, 19 x 300 mm, flow rate 30 mL/min, eluting with water with 0.1% TFA/acetonitrile (19:1 to 1:1 gradient)] followed by SCX chromatography to obtain the free base of the title

compound. Use a method similar to the General Procedure 2-1 to obtain the title compound (120 mg, 28% yield over 3 steps). MS (ES+) *m/z*: 279.2 $(M+H)^+$.

Example 664

6-(4-*tert*-Butylcarbamoyl-benzylthio)-7-chloro-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

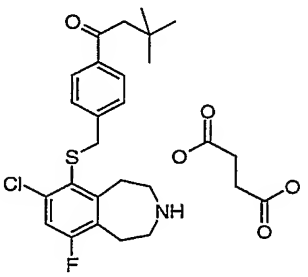


Use a method similar to Example 456 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 4-chloromethyl-*N*-(*tert*-butyl)-benzamide.

Use methods similar to the General Procedures 1-5 and 2-1 to give the title compound as a white solid. MS (ES+) *m/z*: 421 $(M+H)^+$.

Example 665

7-Chloro-6-[4-(3,3-dimethylbutyryl)-benzylthio]-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

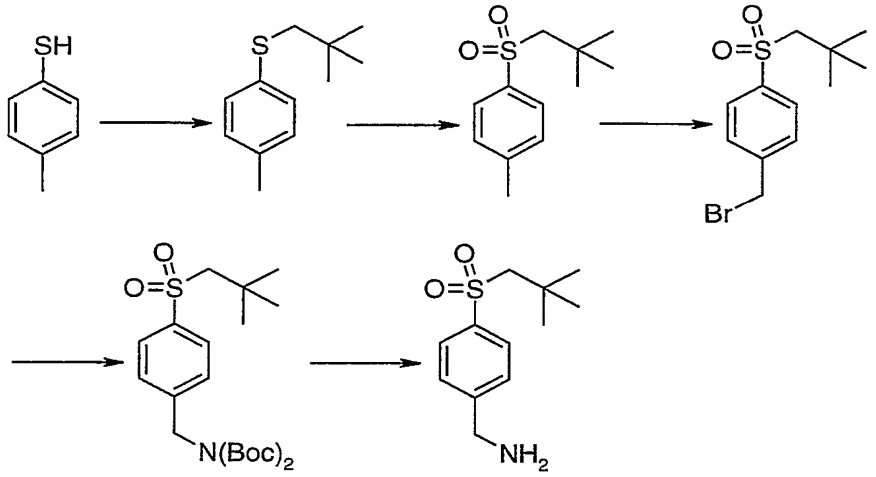


Use a method similar to Example 435 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-9-fluoro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 1-(4-bromomethylphenyl)-3,3-dimethylbutan-1-one.

Use methods similar to the General Procedures 1-5 and 2-2 to give the title compound as a white solid. MS (ES+) *m/z*: 420 $(M+H)^+$.

Preparation 346

4-(2,2-Dimethyl-propane-1-sulfonyl)-



benzylamine

1-(2,2-Dimethyl-propylthio)-4-methyl-benzene: Dissolve 4-methyl-benzenethiol (1.5 g, 12.08 mmol) in anhydrous DMF (6 mL). Cool the solution to 0°C, add sodium hydride (435 mg, 17.21 mmol, 95%) and stir the mixture under nitrogen atmosphere for 15 min. Add 1-iodo-2,2-dimethylpropane (1.93 mL, 14.5 mmol), stir the mixture for 1 h at 0°C, warm to room temperature and stir overnight. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts twice with iced-water, dry over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (1.476 g, 63% yield).

1-(2,2-Dimethyl-propane-1-sulfonyl)-4-methyl-benzene: Dissolve 1-(2,2-dimethyl-propylthio)-4-methyl-benzene (1.476 g, 7.6 mmol) in trifluoroacetic acid (9.5 mL). Add dropwise hydrogen peroxide (9.9 mL, 30% in water), cool the mixture to 0°C and stir 15 min at this temperature and 45 min at room temperature. Concentrate the mixture *in vacuo*, dilute with saturated aqueous $NaHCO_3$ and extract the aqueous phase twice with

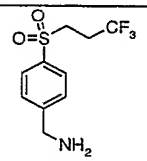
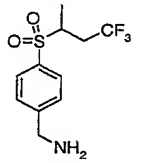
EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (1.548 g, 90%).

1-Bromomethyl-4-(2,2-dimethyl-propane-1-sulfonyl)-benzene: Use a method similar to the Preparation 213 (Step 2), using 1-(2,2-dimethyl-propane-1-sulfonyl)-4-methyl-benzene (560 mg, 2.47 mmol) to give the desired intermediate.

***N*-(di-*tert*-Butoxycarbonyl)-4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamine:** Add sodium hydride (60 mg, 2.39 mmol) to a solution of di-*tert*-butyl-iminodicarboxylate (519 mg, 2.39 mmol) in anhydrous DMF (2mL) at room temperature under nitrogen and stir for 15 min. Then add a solution of 1-bromomethyl-4-(2,2-dimethyl-propane-1-sulfonyl)-benzene (731 mg, 2.39 mmol) in anhydrous DMF (3 mL) and stir for 1.5 h. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts with iced-water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (88:12) to obtain the desired intermediate (460 mg, 44% over 2 steps).

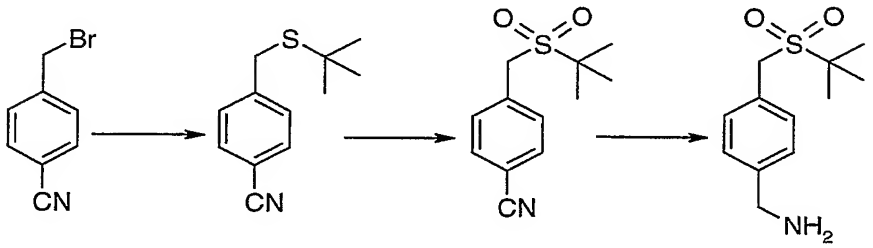
4-(2,2-Dimethyl-propane-1-sulfonyl)-benzylamine: Add 4N hydrogen chloride in dioxane (2 mL) to a solution of *N*-(di-*tert*-butoxycarbonyl)-4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamine (460 mg, 1.04 mmol) in dichloromethane (20 mL) and stir overnight. Concentrate *in vacuo*, suspend the solid obtained in EtOAc, add saturated aqueous $NaHCO_3$ and stir until both phases are clear. Extract the aqueous phase three times with dichoromethane EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to obtain the title compound as an oil that was used without any further purification (166 mg, 71% yield). MS (ES+) *m/z*: 242 $(M+H)^+$.

The compounds of Preparations 347-348 may be prepared essentially as described in Preparation 346 using 1-iodo-3,3,3-trifluoropropane (Preparation 347) or 1,1,1-trifluoro-3-iodobutane (Preparation 348). MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	MS (ES+) *m/z*
347		4-(3,3,3-Trifluoro-propane-1-sulfonyl)-benzylamine	268 $(M+H)^+$
348		4-(4,4,4-Trifluoro-butane-2-sulfonyl)-benzylamine	282 $(M+H)^+$

Preparation 349

4-(2-Methyl-propane-2-sulfonylmethyl)-benzylamine

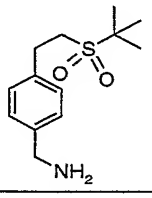


4-*tert*-Butylthiomethyl-benzonitrile: Add sodium hydride (359 mg, 14.21 mmol) to a solution of 2-methyl-2-propanethiol (900 mg, 9.98 mmol) in anhydrous DMF (15 mL) under nitrogen. Stir the mixture for 15 min, add 4-bromomethyl-benzonitrile (2.348 g, 11.97 mmol) and stir the resulting mixture overnight at room temperature. Add water and extract the aqueous phase twice with EtOAc. Wash the combined organic extracts twice with iced-water, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc 92:8 to give the desired intermediate (1.42 g, 69% yield).

4-(2-Methyl-propane-2-sulfonylmethyl)-benzonitrile: Dissolve 4-*tert*-butylthiomethyl-benzonitrile (1.42 g, 6.9 mmol) in trifluoroacetic acid (9 mL). Add dropwise hydrogen peroxide (9 mL, 30% in water), cool the mixture to 0°C and stir 15 min at this temperature and 45 min at room temperature. Concentrate the mixture *in vacuo*, dilute with saturated aqueous $NaHCO_3$ and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the desired intermediate (1.46 g, 89%).

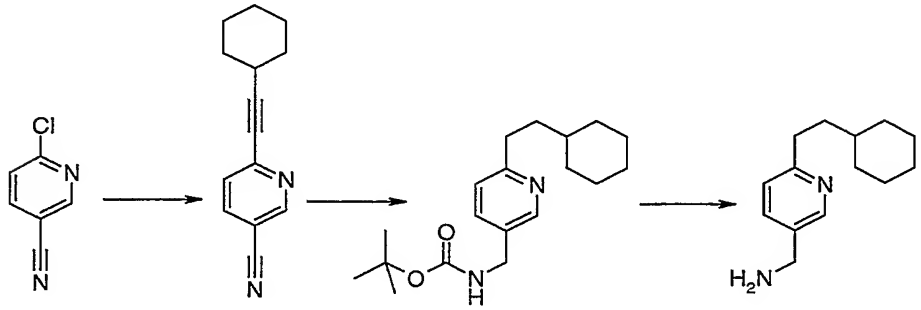
4-(2-Methyl-propane-2-sulfonylmethyl)-benzylamine: Dissolve 4-(2-methyl-propane-2-sulfonylmethyl)-benzonitrile (300 mg, 1.26 mmol) in methanol (50 mL). Add concentrated HCl (10 drops), 10% Pd/C (Degussa type E101, 60 mg) and submit the mixture to hydrogenation at atmospheric pressure for 1 h. Filter over Celite® and wash with methanol. Concentrate the filtrate *in vacuo* to give the hydrochloride salt of the title compound as a solid that was washed with diethyl ether (366 mg, 87%). Partition the solid between saturated $NaHCO_3$ and EtOAc and extract the aqueous phase twice with EtOAc. Dry the combined organic extracts over Na_2SO_4, filter and concentrate *in vacuo* to give the title compound (195 mg, 74%). MS (ES+) *m/z*: 242 $(M+H)^+$.

The compound of Preparation 350 may be prepared essentially as described in Preparation 349 using 4-(2-bromo-ethyl)-benzonitrile. MS (ES+) data are shown in the Table below.

Prep.	Structure	Compound	MS (ES+) *m/z*
350		4-[2-(2-Methyl-propane-2-sulfonyl)-ethyl]-benzylamine	256 $(M+H)^+$

Preparation 351

3-Aminomethyl-6-(2-cyclohexyl-ethyl)-pyridine



6-Cyclohexylethynyl-nicotinonitrile: Add cyclohexylacetylene (1.54 mL, 11.6 mmol), dichlorobis(triphenylphosphine)palladium (200 mg, 0.28 mmol), copper iodide (100 mg,

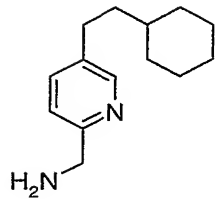
0.53 mmol), and triethylamine (2.0 mL, 14.3 mmol) to a solution of 6-chloronicotinonitrile (1.38 g, 9.9 mmol) in DMF (4 mL). Heat the mixture in a sealed flask for 3 h at 100 °C. Cool the mixture to room temperature, dilute with 1:1 hexane/EtOAc (100 mL) and wash with an aqueous 10% sodium chloride solution (3 x 30 mL). Collect the organic layer, concentrate *in vacuo*, and purify the residue by silica gel chromatography (90 g silica, hexane / EtOAc 95/5 to 85/15 gradient) to obtain the desired intermediate (1.75 g, 83%)

3-*tert*-Butoxycarbonyl-aminomethyl-6-(2-cyclohexyl-ethyl)-pyridine: Add 6-cyclohexylethynyl-nicotinonitrile (1.75 g, 8.3 mmol), 10% Pd/c (Degussa type E101, 50% water by wt) (1.0 g), methanol (100 mL), and di-*t*-butyl dicarbonate (2.3 g, 10.4 mmol) to a pressure vessel under a nitrogen atmosphere. Pressurize the vessel to 30 psi with hydrogen, and stir the mixture for 3 h (monitor the reaction by TLC). Purge the vessel with nitrogen, filter the mixture through Celite® and wash the cake with dichloromethane under a nitrogen atmosphere. Concentrate the filtrate *in vacuo*. Purify the residue by silica gel chromatography (90 g silica, hexane / EtOAc, 95/5 to 50/50 gradient) to obtain the desired intermediate (1.05 mg, 40%). MS (ES+) *m/z*: 319.2 $(M+H)^+$.

3-Aminomethyl-6-(2-cyclohexyl-ethyl)-pyridine: Add trifluoroacetic acid (2.0 mL) to a solution of 3-*tert*-butoxycarbonyl-aminomethyl-6-(2-cyclohexyl-ethyl)-pyridine (1.05 g, 3.3 mmol) in methanol (20 mL). Stir the solution for 1 h at room temperature under a nitrogen atmosphere. Concentrate the solution *in vacuo* and purify the residue via SCX chromatography to obtain the desired intermediate (670 mg, 93 %). MS (ES+) *m/z*: 219.2 $(M+H)^+$.

Preparation 352

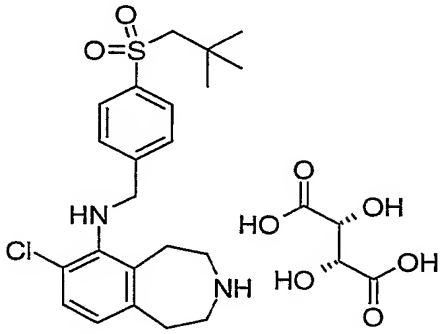
2-Aminomethyl-5-(2-cyclohexyl-ethyl)-pyridine



The title compound may be prepared essentially as described in Preparation 351 by using 5-chloro-pyridine-2-carbonitrile (24% yield, MS (ES) *m/z* 219.2 $(M+H)^+$.

Example 666

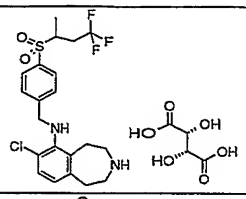
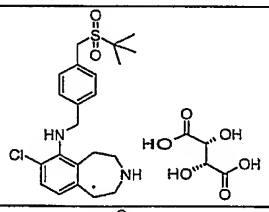
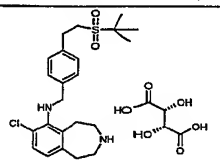
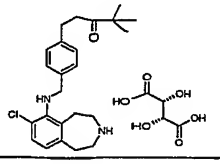
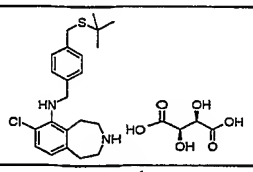
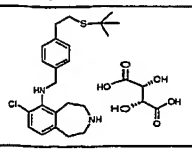
7-Chloro-6-[4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (*L*)-Tartrate

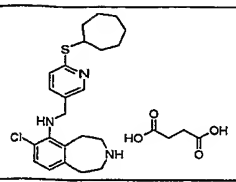
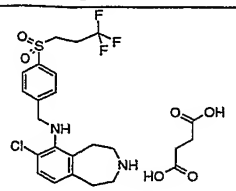


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (158 mg, 0.37 mmol) with 4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamine (166 mg, 0.73 mmol) by using tris(dibenzylideneacetone)dipalladium(0) (68 mg, 0.074 mmol), BINAP (92 mg, 0.148 mmol) and cesium carbonate (169 mg, 0.518 mmol) in anhydrous toluene (15 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (8:2) and then by reversed HPLC [Zorbax Bonus RP, 5 □M 21.2 x 100 mm, eluting with water/acetonitrile (0.05% TFA in each), UV detector (230 nm)] to give 7-chloro-6-[4-(2,2-dimethyl-propane-1-sulfonyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (153 mg, 80%). MS (ES+) *m/z*: 517 $(M+H)^+$.

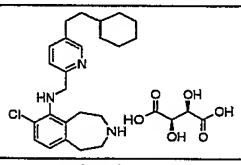
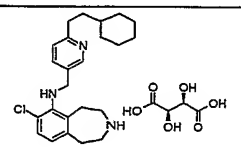
Use methods similar to the General Procedures 1-2 and 2-6 to give the title compound as a white solid. MS (ES+) *m/z*: 421 $(M+H)^+$.

Examples 667-672 may be prepared essentially as described in Example 666 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Examples 673-674 may be prepared essentially as described in Example 666 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine but the succinate salt was prepared as described in General Procedure 2-1. MS (ES+) data are shown in the Table below.

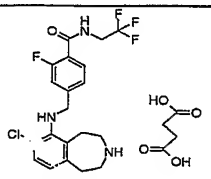
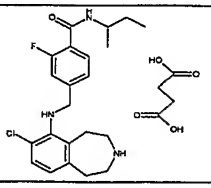
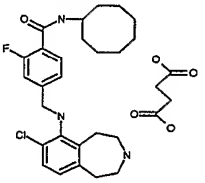
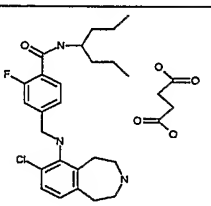
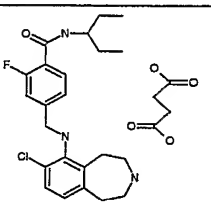
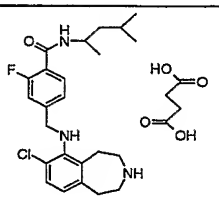
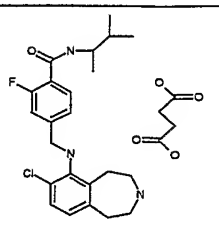
Ex.	Structure	Compound	MS (ES+) *m/z*
667		7-Chloro-6-[4-(4,4,4-trifluorobutane-2-sulfonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	461 $(M+H)^+$
668		7-Chloro-6-[4-(2-methyl-propane-2-sulfonylmethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	421 $(M+H)^+$
669		7-Chloro-6-[4-(2-methyl-propane-2-sulfonylethyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	435 $(M+H)^+$
670		7-Chloro-6-[4-(4,4-dimethyl-3-oxo-pentyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	399 $(M+H)^+$
671		7-Chloro-6-[4-(t-butylthiomethyl-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	389 $(M+H)^+$
672		7-Chloro-6-[4-(t-butylthioethyl-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	403 $(M+H)^+$

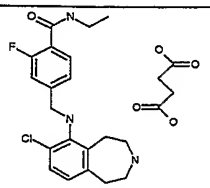
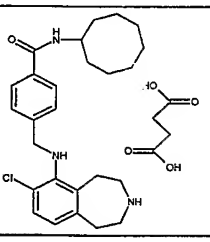
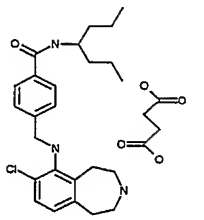
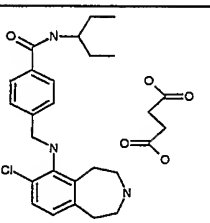
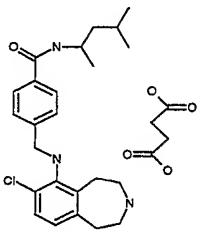
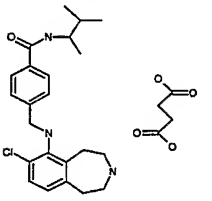
673		7-Chloro-6-[(6-cycloheptylthio-pyridin-3-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	416 $(M+H)^+$
674		7-Chloro-6-[4-(3,3,3-trifluoropropane-1-sulfonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	447 $(M+H)^+$

Examples 675-676 may be prepared essentially as described in Example 604 using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine but the (L)-tartrate salt was prepared as described in General Procedure 2-6. MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	MS (ES+) *m/z*
675		7-Chloro-6-(5-cyclohexylethyl-pyridin-2-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	398 $(M+H)^+$
676		7-Chloro-6-(6-cyclohexylethyl-pyridin-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (L)-Tartrate	398 $(M+H)^+$

Examples 677-684 may be prepared essentially as described in Example 563 by using 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Examples 685-689 may be prepared essentially as described in Example 563 by using 3-*tert*-butoxycarbonyl-6-(4-carboxy-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. MS (ES+) data are shown in the Table below.

Ex.	Structure	Compound	MS (ES+) *m/z*
677		7-Chloro-6-[4-(2,2,2-trifluoroethylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	430 $(M+H)^+$
678		7-Chloro-6-[4-(2-butylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	404 $(M+H)^+$
679		7-Chloro-6-[4-(2-cycloheptylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	458 $(M+H)^+$
680		7-Chloro-6-[4-(4-heptylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	446 $(M+H)^+$
681		7-Chloro-6-[4-(3-pentylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	418 $(M+H)^+$
682		7-Chloro-6-[4-(4-methyl-2-pentylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	432 $(M+H)^+$
683		7-Chloro-6-[4-(3-methyl-2-butylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	418 $(M+H)^+$

684		7-Chloro-6-[4-(ethylcarbamoyl)-3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	376 $(M+H)^+$
685		7-Chloro-6-[4-(2-cycloheptylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	440 $(M+H)^+$
686		7-Chloro-6-[4-(4-heptylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	428 $(M+H)^+$
687		7-Chloro-6-[4-(3-pentylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	400 $(M+H)^+$
688		7-Chloro-6-[4-(4-methyl-2-pentylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	414 $(M+H)^+$
689		7-Chloro-6-[4-(3-methyl-2-butylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	400 $(M+H)^+$

The compounds of the present invention are relatively selective for the 5-HT_{2C} receptor. The compounds of the present invention are particularly relatively selective for the 5-HT_{2C} receptor in comparison to other 5-HT receptor subtypes and specifically the

5-HT_{2A} and 5-HT_{2B} receptors. This selectivity is demonstrated in the following agonist activity assays and receptor binding assays.

Agonist Activity Assays (G alpha q-GTPγ[^{35}S] Binding Assays)

The 5-HT_2 receptors are functionally coupled to specific G-proteins. Agonist activation of 5-HT_2 G-protein-coupled receptors results in the release of GDP from the α-subunit (G alpha q or G alpha i) of the G-protein and the subsequent binding of GTP. The binding of the stable analog GTPγ[^{35}S] is an indicator of receptor activation (i.e. agonist activity).

The G alpha q-GTPγ[^{35}S] binding assay is used to determine the in vitro potency (EC_{50}) and maximal efficacy (E_{max}, normalized to the 5-HT response) of a test compound at the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. The area under the dose response curve (AUC) is also determined for each receptor subtype and used to measure the test compound's selectivity for the 5-HT_{2C} receptor over the 5-HT_{2A} and 5-HT_{2B} receptors, expressed as Selectivity Ratios (AUC 2C/2A and AUC 2C/2B, respectively). The Selectivity Ratios allow the assessment of selectivity based on both potency and efficacy. A selectivity measure that incorporates both potency and efficacy at the 5-HT_{2C} receptor, as compared to the 5-HT_{2A} and 5-HT_{2B}.receptors, is considered important due to the adverse events associated with 5-HT_{2A} and 5-HT_{2B} agonist activity (see introduction).

Membrane Preparation: Grow AV12 cells stably transfected with the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptors in suspension, harvest by centrifugation, wash the cell pellet with phosphate buffered saline, pH 7.4, pellet the cells again, remove the supernatant, freeze the cell pellet on dry ice and store at -70°C. Thaw stock cell pellet and resuspend in 50mM Tris, pH 7.4, aliquot into 1-2 mL volumes and refreeze at -70°C for subsequent assays. (As is appreciated in the art, optimal cell quantities used per aliquot will vary with the individual transfected cell line used. In one embodiment, 5-HT_{2A} and 5-HT_{2C} transfected cells are typically used at about 6×10^8 cells per aliquot, while 5-HT_{2B} cells are typically used at about 7.5×10^8 cells per aliquot).

On the day of assay, thaw membranes, wash the membranes with assay buffer (50 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 100 mM NaCl, and 0.2 mM EDTA), resuspend in assay buffer and incubate for 10 min. at 37°C to hydrolyze any residual endogenous 5-HT. Wash the membranes again with assay buffer, and resuspend in assay buffer at a concentration to provide aliquots of about 1-4x10^6 cell equivalents per well (typically about 1-2 x 10^6 cell equivalents for assays with 5-HT_{2A} or 5-HT_{2C} receptor assays, and about 3-4 x 10^6 cell equivalents for assays with 5-HT_{2B} receptor assays). Homogenize the cells with a tissue grinder and use the homogenate directly in the assay as described below.

G alpha q-GTPγ[^{35}S] Binding Assays: The immunoadsorption scintillation proximity assay (ISPA) of [^{35}S]-GTPγS binding to G alpha q is modified from published conditions (DeLapp et al, JPET **289** (1999) 946-955). Dissolve test compounds in DMSO and dilute in assay buffer to provide a range of concentrations to generate a concentration response curve. In wells of a 96 well microtiter plate, mix diluted test compound, GDP (0.1 μM final concentration), and [^{35}S]-GTPγS (between 0.5 and 1.0 nM final concentration). Add an aliquot of membranes to the incubation mixture and mix the plates to initiate agonist stimulation of the nucleotide exchange (200 μl final volume). Incubate the microtiter plates for 30 min. at room temperature. Quench the incubation with IGEPAL® CA-630 detergent (0.27% final concentration). Add affinity purified polyclonal rabbit anti-G alpha q antibody (about 1-2 μg per well), and anti-rabbit Ig scintillation proximity assay beads (Amersham; about 1.25 mg per well; 300 μl final volume). Seal the plates and incubate the mixture for 3 h at room temperature. Centrifuge the microtiter plates briefly to pellet beads. Quantitate the GTPγ[^{35}S] binding by microtiter plate scintillation spectrometry (Wallac Trilux MicroBeta™ scintillation counter).

Data Analysis: For each concentration response curve for a test compound at a given receptor, analyze the data with GraphPad Prism™ software (v3.02; GraphPad Software, San Diego, CA) running on a personal computer with MicroSoft Windows

OS®, using nonlinear regression analysis curve fitting to determine the EC_{50} and E_{max} (normalized to 5-HT control curves). Determine the Area Under the agonist concentration-response Curve (AUC) with GraphPad Prism™ by the trapezoidal method.

To calculate the Selectivity Ratios, first, determine the AUC for the test compound for each receptor subtype as described above. Second, normalize the AUC's at each receptor subtype relative to the AUC determined for 5-HT at that receptor. The normalized AUC for a test compound at a given receptor is therefore expressed as a percentage of the AUC determined for 5-HT at that receptor. For example:

$$5HT_{2A}\text{ Normalized AUC} = a = \frac{(AUC_{\text{test compound}}\text{ at }5HT_{2A}\text{ receptor})}{(AUC_{5\text{-HT}}\text{ at }5HT_{2A}\text{ receptor})} \times 100\%$$

$$5HT_{2B}\text{ Normalized AUC} = b = \frac{(AUC_{\text{test compound}}\text{ at }5HT_{2B}\text{ receptor})}{(AUC_{5\text{-HT}}\text{ at }5HT_{2B}\text{ receptor})} \times 100\%$$

$$5HT_{2C}\text{ Normalized AUC} = c = \frac{(AUC_{\text{test compound}}\text{ at }5HT_{2C}\text{ receptor})}{(AUC_{5\text{-HT}}\text{ at }5HT_{2C}\text{ receptor})} \times 100\%$$

Third, calculate the Selectivity Ratios for the test compound as follows:

Selectivity Ratio for 5-HT_{2C} receptor/5-HT_{2A} receptor (AUC 2C/2A) = c/a

Selectivity Ratio for 5-HT_{2C} receptor/5-HT_{2B} receptor (AUC 2C/2B) = c/b

For reference purposes, the AUC 2C/2A and AUC 2C/2B for 5-HT are each 1.0. Likewise, the ratios for mCPP (*meta*-chlorophenylpiperazine) are tested and are found to be 2.1 and 2.1 respectively.

Representative compounds of the present invention are tested in the G alpha q-GTPγ[^{35}S] assays for the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors essentially as described above and are found to be a highly potent and selective agonists of the 5-HT_{2C} receptor, with EC_{50}'s typically less than or equal to 200 nM, and AUC 2C/2A and AUC 2C/2B ratios greater than 1.5. Preferred compounds are those with EC50's less than or equal to 100 nM, and AUC 2C/2A and AUC 2C/2B ratios greater than or equal to 2.0. More preferred are those with EC50's less than or equal to 50 nM, and AUC 2C/2A and AUC 2C/2B ratios greater than or equal to 3.0.

Ligand Binding Assays

The ligand binding affinity of the compounds of the present invention to the 5-HT_{2C} receptor subtype is measured essentially as described by Wainscott (Wainscott, *et al.*, *Journal of Pharmacology and Experimental Therapeutics*, 276:720-727 (1996)). Data is analyzed by nonlinear regression analysis on the concentration response curves using the four parameter logistic equation described by DeLean (DeLean, et al., Molecular Pharmacology, **21**, 5-16 (1982)). IC_{50} values are converted to K_i values using the Cheng-Prusoff equation (Cheng, et al., Biochem. Pharmacol., **22**, 3099-3108 (1973)).

Representative compounds of the present invention are tested essentially as described above and are found to have excellent affinity for the 5-HT_{2C} receptor, with K_i's typically less than or equal to about 200 nM. Preferred compounds are those with K_i's of less than or equal to about 100 nM. More preferred are those with K_i's less than or equal to 50 nM.

Affinities for other receptor subtypes can readily be determined by slight modification of the above described radioligand receptor binding assay using cells transfected with the desired receptor in place of cells transfected with the 5-HT_{2C} receptor subtype and using an appropriate radioligand. The binding affinities for representative compounds of the present invention for a variety of receptors are determined in such assays and the compounds are found to have surprisingly higher affinity for the 5-HT_{2C} receptor. Affinity for the 5-HT_{2C} receptor is found to be significantly higher than for other 5-HT receptor subtypes, and notably higher than the 5-HT_{2A} and 5-HT_{2B} receptor subtypes. Preferred compounds are those with IC_{50}'s equal to or greater than 300 nM for the alpha 1 and alpha 2 adrenergic receptors and equal to or greater than 500 nM for D_1 and D_2 dopaminergic receptors. More preferred compounds are those with IC_{50}'s equal to or greater than 1000 nM for the alpha 1 and alpha 2 adrenergic receptors and the D_1 and D_2 dopaminergic receptors. Still more preferred are those compounds with IC_{50}'s equal to or greater than 3000 nM for the alpha 1 and alpha 2 adrenergic receptors and the D_1 and D_2 dopaminergic receptors.

For the above in vitro assays, exemplified compounds are assayed and found to have either an EC_{50} or a K_i value of equal to or less than 50 nM, and to have AUC 2C/2A and AUC 2C/2B ratios of greater than or equal to 2.0. Exemplified compounds are assayed and found to have alpha 1 and alpha 2 adrenergic receptor IC_{50}'s equal to or greater than 300 nM, and D_1 and D_2 dopaminergic receptor IC_{50}'s equal to or greater than 500 nM.

Rat feeding assays

The ability of the compounds of the present invention to treat obesity is demonstrated by testing in acute and chronic rat feeding assays.

Animals: Obtain male Long-Evans rats (Harlan Sprague-Dawley, Indianapolis, IN) that are approximately one hundred-days old and have been maintained on a calorie rich diet since weaning (TD 95217, 40% calories from fat; Teklad, Madison, WI). House the rats individually with a 12 h:12 h light:dark cycle (lights on from about 22:00 h to about 10:00 h) and maintain rats on the same diet (TD 95217) with free access to water, for about 1-2 weeks to acclimate the rats to the environment. Dose rats orally with vehicle (10% acacia with 0.15% saccharin in water) once daily for at least 1 day (typically 1-2 days) to acclimate the rats to the procedures. Randomize the rats into groups so each group has similar mean body weights.

Calorimetric Acute Feeding Assay: At approximately 8:00 h on the day of assay, weigh each rat and transfer to individual chambers of an open circuit calorimetry system (Oxymax, Columbus Instruments International Corporation; Columbus, OH), with free access to food (pre-weighed) and water, and begin measuring VO_2 and VCO_2. At approximately 10:00 h, dose rats orally with vehicle or test compound, return them to their calorimetry chambers, and continue measuring VO_2 and VCO_2 at regular time intervals (approximately hourly). At approximately 8:00 h the following day, measure rat body weight and the remaining food, assuming the difference in weight of food is equal to the mass of food consumed. Calculate the 24 h energy expenditure (EE) and respiratory

quotient (RQ) essentially as described in Chen, Y. and Heiman, M. L., Regulatory Peptide, 92:113-119 (2000). EE during light photoperiod is indicative of the resting metabolic rate and RQ is indicative of the fuel source the animal utilizes (pure carbohydrate metabolism gives an RQ of about 1.0, pure fat metabolism gives an RQ of about 0.7, mixed carbohydrate and fat metabolism gives intermediate values for RQ). Calculate EE as the product of calorific value (CV) and VO_2 per body weight (kg); where CV = 3.815 + 1.232*RQ, and RQ is the ratio of CO_2 produced (VCO_2) to O_2 consumed (VO_2). Caloric intake is calculated as (mass of 24 h food intake in grams) x (physiological fuel value of the diet in kilocalorie/g) per kg of body weight.

Acute Feeding Assay with a selective 5-HT_{2C} receptor antagonist: The above calorimetric acute feeding assay is conducted with the following modifications. Open circuit calorimetry systems are not used and only the 24 h periodic food intake and body weight are measured. Three groups of rats are used with the first group receiving a subcutaneous dose of saline (0.5 mL) about 15 minutes prior to the oral dose of vehicle, the second group receiving a subcutaneous dose of saline (0.5 mL) about 15 minutes prior to the oral dose of test compound in vehicle, and the third group receiving a subcutaneous injection of a selective 5-HT_{2C} receptor antagonist, 6-chloro-5-methyl-N-{2-[(2-methylpyridin-3-yl-oxy)pyridin-5-yl]aminocarbonyl}-2,3-dihydroindole (3 mg/Kg, in 35% cyclodextrin, 0.5 mL), about 15 min. prior to the oral dose of test compound in vehicle.

Chronic Feeding Assay: At between approximately 8:00 h and 10:00 h on day one of the assay, weigh and orally dose each rat with vehicle or test compound and return the animal to its home cage, with free access to food (pre-weighed) and water. For each of days 2-15, at between approximately 8:00 h and 10:00 h, measure rat body weight and the weight of food consumed in the last 24 h period, and administer daily oral dose of test compound or vehicle. On days –2 and 15 measure total fat mass and lean mass by nuclear magnetic resonance (NMR) using an EchoMRI™ system (Echo Medical Systems, Houston Texas). (See Frank C. Tinsley, Gersh Z. Taicher, and Mark L. Heiman, "Evaluation of a New

Quantitative Magnetic Resonance (QMR) Method for Mouse Whole Body Composition Analysis", Obesity Research, submitted May 1, 2003.)

Representative compounds of the present invention are tested in acute and chronic feeding assays essentially as described above. In the acute assays, the compounds are found to significantly reduce 24 h food intake, which effect is blocked by pre-administration of the 5-HT_{2C} receptor antagonist. The compounds also are found to dose-dependently reduce RQ without significantly changing the energy expenditure during the light photo-period. Thus the compounds are found to reduce caloric intake and increase the proportion of fuel deriving from fat utilization, without significantly changing the resting metabolic rate. In the chronic assay, the compounds are found to significantly decrease cumulative food intake and cumulative body weight change in a dose-dependent manner compared to control animals. The decrease in body weight is found to be due to loss of adipose tissue while lean body mass is not changed.

The ability of the 5-HT_{2C} receptor agonists of the present invention to treat obsessive/compulsive disorder is demonstrated by testing in a variety of in vivo assays as follows:

Marble burying assay

Marble burying in mice has been used to model anxiety disorders including obsessive-compulsive disorders (OCD) due to ethological study of the behavior (e.g. Gyertyan I. "Analysis of the marble burying response: Marbles serve to measure digging rather than evoke burying", *Behavioural Pharmacology* 6: 24-31, (1995)) and due to the pharmacological effects of clinical standards (c.f., Njung'E K. Handley SL. "Evaluation of marble-burying behavior as a model of anxiety", *Pharmacology, Biochemistry & Behavior.* 38: 63-67, (1991)); Borsini F., Podhorna J., and Marazziti, D. "Do animal models of anxiety predict anxiolytic effects of antidepressants?", *Psychopharmacology* 163: 121-141, (2002)). Thus, drugs used in the treatment of generalized anxiety in humans (e.g. benzodiazepines) as well as compounds used to treat OCD (e.g. SSRIs like fluoxetine) decrease burying.

House experimentally-naïve male, NIH Swiss mice (Harlan Sprague-Dawley, Indianapolis, IN) weighing between 28-35 g in groups of 12 for at least three days prior to testing in a vivarium with 12 h light and dark cycles. Conduct experiments during the light cycle in a dimly lit experimental testing room. Dose mice with vehicle or test compound and, after a specified pretreatment interval (generally 30 min.), place each mouse individually on a rotorod (Ugo Basile 7650) operating at a speed of 6 revolutions/min. and observe for falling. After 2 min. on the rotorod, place the mice individually in a 17 x 28 x 12 cm high plastic tub with 5 mm sawdust shavings on the floor that are covered with 20 blue marbles (1.5 cm diameter) placed in the center. After 30 min., count the number of marbles buried (2/3 covered with sawdust). Assess the test compound's effect on marble burying with Dunnett's test and the effect on rotorod performance by Fisher's exact test.

Clinically effective standard compounds suppress marble burying at doses that are devoid of motor-impairing effects as measured on the rotorod. The *in vivo* efficacy of $5HT_{2C}$ compounds at the $5HT_{2C}$ receptor is confirmed by the prevention of effects of the $5HT_{2C}$ agonists on marble burying by co-administration of the $5HT_{2C}$ receptor antagonist, 6-chloro-5-methyl-N-{2-[(2-methylpyridin-3-yl-oxy)pyridin-5-yl]aminocarbonyl}-2,3-dihydroindole.

Representative compounds of the present invention are assayed in the marble burying assay essentially as described and are surprisingly found to reduce burying behavior in the test mice. The reduction of burying behavior is found to be blocked by co-administration of the 5-HT_{2C} antagonist. In contrast to the compounds of the present invention, the anxiolytic compound chlordiazepoxide and the antipsychotic compound chlorpromazine decrease marble burying only at doses that also disrupt rotorod performance.

Nestlet Shredding

Mice naturally will construct nests of material available in their living environment. Since this behavior is obsessive in nature, it has been used to model OCD (Xia Li, Denise Morrow and Jeffrey M. Witkin, "Decreases in nestlet shredding of mice by serotonin uptake inhibitors: comparison with marble burying", Psychopharmacology, submitted July 14, 2003). House experimentally-naïve male, NIH Swiss mice (Harlan Sprague-Dawley, Indianapolis, IN) weighing between 28-35 g in groups of 12 for at least three days prior to testing in a vivarium with a 12 h light/dark cycle. Conduct experiments during the light cycle in an experimental room with normal overhead fluorescent lighting. Dose mice with vehicle or test compound and after a specified pretreatment interval (generally 30 min.), place the mice individually in a 17 x 28 x 12 cm high plastic tub with about 5 mm sawdust shavings on the floor along with a pre-weighed multi-ply gauze pad (51 mm square). After 30 min., weigh the remainder of the gauze pad not removed by the mouse. Determine the weight of the gauze used for nestlet construction by subtraction. Compare the results for test compound treated mice to the results for vehicle control treated mice with Dunnett's test.

Clinically effective OCD treatment standard compounds suppress nestlet shredding at doses that are devoid of motor-impairing effects as measured by the rotorod test. The *in vivo* efficacy of $5HT_{2C}$ compounds at the $5HT_{2C}$ receptor is confirmed by the prevention of effects of the $5HT_{2C}$ agonists on nestlet shredding by co-administration of the $5HT_{2C}$ receptor antagonist, 6-chloro-5-methyl-N-{2-[(2-methylpyridin-3-yl-oxy)pyridin-5-yl]aminocarbonyl}-2,3-dihydroindole.

Representative compounds of the present invention are assayed essentially as described above and are surprisingly found to suppress nestlet shredding at doses that are devoid of motor-impairing effects as measured by the rotorod test.

In contrast to the compounds of the present invention, the anxiolytic chlordiazepoxide and the psychomotor stimulant d-amphetamine decreases nestlet shredding only at doses that produce motoric side effects (depression or stimulation, respectively).

Schedule-Induced Polydipsia

Food-deprived rats exposed to intermittent presentations of food will drink amounts of water that are far in excess of their normal daily intake and in excess of their intake when given all of their food at one time (Falk JL. "Production of polydipsia in normal rats by an intermittent food schedule", *Science* 133: 195-196, (1961)). This excessive behavior is persistent and has been used to model OCD.

Maintain Wistar rats on a food restricted diet (to maintain 85% free feeding weight), but with free access to water. Train the rats in a behavioral testing chamber to press a lever to receive a food pellet under a fixed interval schedule, such that the rats are rewarded with a 45 mg food pellet the first time they press a lever after a 120 second interval has elapsed. The fixed interval is then reset to 120 seconds and the process repeated. Thus, during a 90 min. test session, the rats can earn a maximum of 45 pellets. The behavioral chamber is also equipped with a water bottle that is weighed before and after the session to determine the amount of water consumed.

Administer test compounds on Tuesdays and Fridays. Determine control day performances on Thursdays. Administer compounds either orally at 60 min. before the beginning of a test session, or subcutaneously at 20 min. before the beginning of a test session. Compare the rates of lever pressing and water consumption for each animal's performance during sessions after test compound treatment with that animal's performance during control sessions, expressed as a percent of the control rate. Average the individual percent of control rates for each dose and calculate the standard error of the mean.

Clinically effective OCD treatment standard compounds (e.g. chlomipramine, fluoxetine) suppress schedule-induced polydipsia without producing notable changes in motor patterns, food intake, or behavior the following day. The *in vivo* efficacy of $5HT_{2C}$ compounds at the $5HT_{2C}$ receptor is confirmed by the prevention of effects of the $5HT_{2C}$ agonists on excessive drinking by co-administration of the $5HT_{2C}$ receptor antagonist, 6-

chloro-5-methyl-N-{2-[(2-methylpyridin-3-yl-oxy)pyridin-5-yl]aminocarbonyl}-2,3-dihydroindole.

Representative compounds of the present invention are assayed in the schedule-induced polydipsia assay essentially as described above and are surprisingly found to suppress schedule-induced polydipsia without producing notable changes in motor patterns, food intake, or behavior the following day. The behavior suppression is blocked by co-administration of the 5-HT_{2C} antagonist.

In contrast to the compounds of the present invention, the psychomotor stimulant d-amphetamine decreases excessive drinking only at behaviorally stimulating doses and these effects are not prevented by the $5HT_{2C}$ receptor antagonist.

While it is possible to administer compounds employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical compositions comprising a pharmaceutically acceptable excipient and at least one compound of Formula I or a pharmaceutically acceptable salt thereof. These compositions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. The compounds employed in the methods of this invention are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art. *See, e.g.* REMINGTON'S PHARMACEUTICAL SCIENCES, (16th ed. 1980).

In making the compositions employed in the present invention the active ingredient is usually mixed with at least one excipient, diluted by at least one excipient, or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound,

soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The compounds are generally effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.01 to about 30 mg/kg. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of

the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Under some circumstances, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by reference.

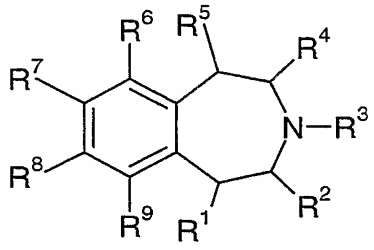
Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced

by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

The type of formulation employed for the administration of the compounds employed in the methods of the present invention may be dictated by the particular compound employed, the type of pharmacokinetic profile desired from the route of administration, and the state of the patient.

WE CLAIM:

1. A compound of Formula I:



I

where:

R^1 is hydrogen, fluoro, or $(C_1\text{-}C_3)$alkyl;

R^2, R^3, and R^4 are each independently hydrogen, methyl, or ethyl;

R^5 is hydrogen, fluoro, methyl, or ethyl;

R^6 is $-C{\equiv}C\text{-}R^{10}$, $-O\text{-}R^{12}$, $-S\text{-}R^{14}$, or $-NR^{24}R^{25}$;

R^7 is hydrogen, halo, cyano, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_2\text{-}C_6)$alkenyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl, $(C_1\text{-}C_6)$alkoxy optionally substituted with 1 to 6 fluoro substituents, $(C_1\text{-}C_6)$alkylthio optionally substituted with 1 to 6 fluoro substituents, $Ph^1\text{-}(C_0\text{-}C_3)$alkyl, $Ph^1\text{-}(C_0\text{-}C_3)$alkyl-O-, or $Ph^1\text{-}(C_0\text{-}C_3)$alkyl-S-;

R^8 is hydrogen, halo, cyano, or $-SCF_3$;

R^9 is hydrogen, halo, cyano, $-CF_3$, $-SCF_3$, or $(C_1\text{-}C_3)$alkoxy optionally substituted with 1 to 6 fluoro substituents;

R^{10} is $-CF_3$, ethyl substituted with 1 to 5 fluoro substituents, $(C_3\text{-}C_6)$ alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, $Ar^1\text{-}(C_0\text{-}C_3)$alkyl, $Ph^1\text{-}(C_0\text{-}C_3)$alkyl, or 3-$(C_1\text{-}C_4)$alkyl-2-oxo-imidazolidin-1-yl-$(C_1\text{-}C_3)$alkyl;

R^{12} is $Ph^2\text{-}(C_1\text{-}C_3)$alkyl, $Ar^2\text{-}(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_6)$alkyl-S-$(C_2\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl-S-$(C_2\text{-}C_6)$alkyl, phenyl-S-$(C_2\text{-}C_6)$alkyl, $Ph^2\text{-}S\text{-}(C_2\text{-}C_6)$alkyl, phenylcarbonyl-$(C_1\text{-}C_3)$alkyl, $Ph^2\text{-}C(O)\text{-}(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl$(C_3\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl-OC(O)-$(C_3\text{-}C_6)$alkyl,

phenyloxycarbonyl-(C_3-C_6)alkyl, Ph^2-OC(O)-(C_3-C_6)alkyl, Ar^2-OC(O)-(C_3-C_6)alkyl, (C_3-C_7)cycloalkyl-NH-C(O)-(C_2-C_4)alkyl-, Ph^1-NH-C(O)-(C_2-C_4)alkyl-, Ar^2-NH-C(O)-(C_2-C_4)alkyl-, or R^{13}-C(O)NH-(C_2-C_4)alkyl;

R^{13} is (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, Ph^1, Ar^2, or (C_1-C_3)alkoxy optionally substituted with 1 to 6 fluoro substituents, Ph^1-NH- or N-linked Het^1;

R^{14} is Ar^2 which is not N-linked to the sulfur atom, Ph^2, R^{15}-L-, tetrahydrofuranyl, tetrahydropyranyl, or phenyl-methyl substituted on the methyl moiety with a substituent selected from the group consisting of (C_1-C_3)-*n*-alkyl substituted with hydroxy, (C_1-C_3)alkyl-O-(C_1-C_2)-*n*-alkyl, (C_1-C_3)alkyl-C(O)-(C_0-C_2)-*n*-alkyl, and (C_1-C_3)alkyl-O-C(O)-(C_0-C_2)-*n*-alkyl,

wherein when R^{14} is Ph^2 or Ar^2, wherein Ar^2 is pyridyl, then R^{14} may also, optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}$N-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents, and

wherein the tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, or with one or two groups independently selected from methyl and –CF_3;

R^{15} is -OR^{16}, cyano, –SCF_3, Ph^2, Ar^2, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalimido, benzothiophenyl optionally substituted at the 2-position with phenyl or benzyl, benzothiazolyl optionally substituted at the 2-position with phenyl or benzyl, benzothiadiazolyl optionally substituted with phenyl or benzyl, 2-oxo-dihydroindol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-dihydroindol-5-yl

optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-imidazolidin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydropyrimidinyl optionally substituted at the 3 or 4 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo-tetrahydroquinolin-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, 2-oxo- dihydrobenzimidazol-1-yl optionally substituted at the 3 position with gem dimethyl or (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, $-NR^{17}R^{18}$, $-C(O)R^{22}$, or a saturated heterocycle selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl, tetrahydrofuranyl, and tetrahydropyranyl,

wherein Ph^2 and Ar^2 when Ar^2 is pyridyl, may also optionally be substituted with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- and phenyl-C≡C- being optionally further substituted on the phenyl moiety with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

wherein Ar^2 may alternatively, optionally be substituted with a substituent selected from the group consisting of (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl, Het^1-(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl, and phenyl-(C_0-C_3)alkyl, and optionally further substituted with one methyl, $-CF_3$, cyano, or $-SCF_3$ substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, $-CH_3$, $-OCH_3$, $-CF_3$, $-OCF_3$, -CN, and $-SCF_3$, and

wherein when Ar^2 is pyridyl, the pyridyl may alternatively, optionally be substituted with $R^{28}R^{29}N$-C(O)-, or (C_1-C_6)alkyl-C(O)- optionally substituted with 1 to 6 fluoro substituents, and may be optionally further

substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents, and

wherein when Ar^2 is thiazolyl, the thiazolyl may alternatively, optionally be substituted with (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-NH-, and

wherein the pyrrolidinyl, piperidinyl, morpholinyl, and thiomorpholinyl is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or is N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkylcarbonyl, (C_1-C_6)alkylsulfonyl,
(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,
(C_3-C_7)cycloalkyl(C_0-C_3)alkyl-$S(O)_2$-, Ph^1-(C_0-C_3)alkyl-C(O)-, and
Ph^1-(C_0-C_3)alkyl-$S(O)_2$-, and

may optionally be further substituted with 1 or 2 methyl or -CF_3 substituents, and when oxo-substituted, may optionally be further N-substituted with a substituent selected from the group consisting of

(C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, and Ph^1-(C_0-C_3)alkyl, and

wherein tetrahydrofuranyl and tetrahydropyranyl may optionally be substituted with an oxo substituent, and/or with one or two groups independently selected from methyl and –CF_3;

L is branched or unbranched (C_1-C_6)alkylene, except when R^{15} is -$NR^{17}R^{18}$ or Ar^2-N-linked to L, in which case L is branched or unbranched (C_2-C_6)alkylene, and when L is methylene or ethylene, L may optionally be substituted with gem-ethano or with 1 to 2 fluoro substituents, and when R^{15} is Ph^2, Ar^2, or a saturated heterocycle, L may alternatively, optionally be substituted with a substituent selected from the group consisting of hydroxy, cyano, -SCF_3, (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents, (C_1-C_6)alkylcarbonyloxy optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-, (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-O-C(O)-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-C(O)-O-;

R^{16} is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_1\text{-}C_6)$alkylcarbonyl, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl-C(O)-, Ph^1-$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_3)$alkyl-C(O)-, Ar^2-$(C_0\text{-}C_3)$alkyl, or Ar^2-$(C_0\text{-}C_3)$alkyl-C(O)-,

R^{17} is $(C_1\text{-}C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, *t*-butylsulfonyl, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl-C(O)-, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl-sulfonyl, Ph^1-$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_3)$alkyl-C(O)-, Ph^1-$(C_0\text{-}C_3)$alkylsulfonyl, Ar^2-$(C_0\text{-}C_3)$alkyl, Ar^2-$(C_0\text{-}C_3)$alkyl-C(O)-, Ar^2-$(C_0\text{-}C_3)$alkylsulfonyl, $R^{19}OC(O)$-, or $R^{20}R^{21}NC(O)$-;

R^{18} is hydrogen or $(C_1\text{-}C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached form Het^1 where Het^1 is substituted with oxo- on a carbon atom adjacent to the ring nitrogen atom, or

R^{17} and R^{18}, taken together with the nitrogen atom to which they are attached, form an aromatic heterocycle selected from the group consisting of pyrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl,

said aromatic heterocycle optionally being substituted with 1 to 2 halo substituents, or substituted with 1 to 2 $(C_1\text{-}C_4)$alkyl substituents optionally further substituted with 1 to 3 fluoro substituents, or mono-substituted with fluoro, nitro, cyano, $-SCF_3$, or $(C_1\text{-}C_4)$alkoxy optionally further substituted with 1 to 3 fluoro substituents, and optionally further substituted with a $(C_1\text{-}C_4)$alkyl substituent optionally further substituted with 1 to 3 fluoro substituents;

R^{19} is $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, Ar^2-$(C_0\text{-}C_3)$alkyl, or Ph^1-$(C_0\text{-}C_3)$alkyl,

R^{20} is $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, Ar^2-$(C_0\text{-}C_3)$alkyl, or Ph^1-$(C_0\text{-}C_3)$alkyl,

R^{21} is hydrogen or $(C_1\text{-}C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{22} is $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, R^{23}-O-, Ph^1-$(C_0\text{-}C_3)$alkyl, Ar^2-$(C_0\text{-}C_3)$alkyl, or $R^{32}R^{33}N$-;

R^{23} is $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_3)$alkyl, or Ar^2-$(C_0\text{-}C_3)$alkyl;

R^{24} is $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_5)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_1\text{-}C_6)$alkylthio$(C_2\text{-}C_5)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_1)$alkyl-O-$(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_1)$alkyl-S-$(C_1\text{-}C_5)$alkyl, phenyl$(C_1\text{-}C_3)$ *n*-alkyl, Ph^2-$(C_1\text{-}C_3)$-*n*-alkyl, $Ar^2(C_0\text{-}C_3)$ *n*-alkyl, phenyl$(C_0\text{-}C_1)$alkyl-O-$(C_1\text{-}C_5)$alkyl, phenyl$(C_0\text{-}C_1)$alkyl-S-$(C_1\text{-}C_5)$alkyl, Ph^1-$(C_0\text{-}C_1)$alkyl-C(O)NH-$(C_2\text{-}C_4)$alkyl, Ph^1-$(C_0\text{-}C_1)$alkyl-NH-C(O)NH-$(C_2\text{-}C_4)$alkyl, pyridyl-$(C_0\text{-}C_1)$alkyl-C(O)NH-$(C_2\text{-}C_4)$alkyl, pyridyl-$(C_0\text{-}C_1)$alkyl-NH-C(O)NH-$(C_2\text{-}C_4)$alkyl, or $Ar^3(C_1\text{-}C_2)$alkyl,

where Ar^3 is a bi-cyclic moiety selected from a group consisting of indanyl, indolyl, dihydrobenzofuranyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzo[1,3]dioxolyl, naphthyl, dihydrobenzopyranyl, quinolinyl, isoquinolinyl, and benzo[1,2,3]thiadiazolyl,

said Ar^3 optionally being substituted with $(C_1\text{-}C_6)$alkyl optionally further substituted with 1 to 6 fluoro substituents, phenyl$(C_0\text{-}C_1)$alkyl optionally further substituted with 1 to 6 fluoro substituents, or substituted with $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, or substituted with 1-3 substituents independently selected from the group consisting of halo, oxo, methyl, and $-CF_3$,

said phenyl$(C_1\text{-}C_3)$ *n*-alkyl, Ph^2-$(C_1\text{-}C_3)$ *n*-alkyl, or $Ar^2(C_0\text{-}C_3)$ *n*-alkyl optionally being substituted on the *n*-alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, gem-ethano, 1 to 2 fluoro substituents, or $(C_1\text{-}C_6)$alkyl-C(O)-,

said $Ar^2(C_0\text{-}C_3)$ *n*-alkyl being alternatively optionally substituted with a substituent selected from the group consisting of $(C_3\text{-}C_7)$cycloalkyl-$(C_0\text{-}C_3)$alkyl, Het^1-$(C_0\text{-}C_3)$alkyl, pyridyl-$(C_0\text{-}C_3)$alkyl, phenyl-

(C_0-C_3)alkyl, pyridyl-(C_0-C_3)alkyl-NH-, phenyl-(C_0-C_3)alkyl-NH-, (C_1-C_6)alkyl-S-, and (C_3-C_7)cycloalkyl-(C_0-C_3)alkyl-S-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said pyridyl-(C_0-C_3)alkyl and phenyl-(C_0-C_3)alkyl optionally being further substituted with 1-3 substituents independently selected from halo, -CH_3, -OCH_3, -CF_3, -OCF_3, -CN, and -SCF_3, and

said Ph^2-(C_1-C_3) *n*-alkyl and Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, also optionally being substituted on the phenyl or Ar^2 moiety, respectively, with phenyl-CH=CH- or phenyl-C≡C-,

said phenyl-CH=CH- or phenyl-C≡C- being optionally further substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, -SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said Ar^2(C_0-C_3) *n*-alkyl where Ar^2 is pyridyl, alternatively, optionally being substituted with (C_1-C_6)alkyl-C(O)- or $R^{28}R^{29}$N-C(O)-, and optionally further substituted with one methyl, -CF_3, cyano, or -SCF_3 substituent, or with 1 to 2 halo substituents,

said phenyl(C_0-C_1)alkyl-O-(C_1-C_5)alkyl, or phenyl(C_0-C_1)alkyl-S-(C_1-C_5)alkyl optionally being substituted on the phenyl moiety with (C_1-C_2)-$S(O)_2$-, or with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, –SCF_3, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and

said pyridyl-(C_0-C_1)alkyl-C(O)NH-(C_2-C_4)alkyl and pyridyl-(C_0-C_1)alkyl-NH-C(O)NH-(C_2-C_4)alkyl optionally being substituted on the pyridyl moiety with methyl, -CF_3, or 1 to 3 halo substituents;

R^{25} is hydrogen, $(C_1\text{-}C_3)$alkyl optionally substituted with 1 to 6 fluoro substituents, or allyl;

R^{26} is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl;

R^{27} is hydrogen or $(C_1\text{-}C_4)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{26} and R^{27}, taken together with the nitrogen atom to which they are attached, form Het^1;

R^{28} is $(C_1\text{-}C_8)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_8)$cycloalkyl$(C_0\text{-}C_3)$alkyl, tetrahydropyran-3-yl$(C_0\text{-}C_3)$alkyl, tetrahydropyran-4-yl$(C_0\text{-}C_3)$alkyl, tetrahydrofuranyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_2)$ *n*-alkyl, or Ar^2-$(C_0\text{-}C_2)$ *n*-alkyl,

said Ph^1-$(C_0\text{-}C_2)$ *n*-alkyl and Ar^2-$(C_0\text{-}C_2)$ *n*-alkyl optionally being substituted on the alkyl moiety when present with $(C_1\text{-}C_3)$alkyl, dimethyl, or gem-ethano;

R^{29} is hydrogen or $(C_1\text{-}C_3)$alkyl;

R^{30} is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl, Ph^1-$(C_0\text{-}C_3)$alkyl, or $Ar^2(C_0\text{-}C_3)$alkyl,

R^{31} is hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{30} and R^{31}, taken together with the nitrogen atom to which they are attached, form Het^1,

said Het^1 also optionally being substituted with phenyl optionally further substituted with 1 to 3 halo substituents;

R^{32} and R^{33} are each independently hydrogen or $(C_1\text{-}C_6)$alkyl optionally substituted with 1 to 6 fluoro substituents, or R^{32} and R^{33}, taken together with the nitrogen atom to which they are attached, form Het^1, or R^{32} is $Ph^1(C_0\text{-}C_1)$alkyl provided that R^{33} is hydrogen;

Ar^1 is an aromatic heterocycle substituent selected from the group consisting of furanyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, and pyridazinyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, $-CF_3$, $-O\text{-}CF_3$, nitro, cyano, and trifluoromethylthio;

Ar^2 is an aromatic heterocycle substituent selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, oxazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyridazinyl, and benzimidazolyl, any of which may optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents, and wherein pyridyl and pyridazinyl may also optionally be substituted with (C_1-C_6)alkylamino optionally further substituted with 1 to 6 fluoro substituents, (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, or (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-amino;

Het^1 is a saturated, nitrogen-containing heterocycle substituent selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, homomorpholinyl, and homothiomorpholinyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents;

Het^2 is a saturated, oxygen-containing heterocycle substituent selected from the group consisting of tetrahydrofuranyl and tetrahydropyranyl, any of which may optionally be substituted with (C_1-C_6)alkyl or with 2 methyl substituents; .

Ph^1 is phenyl optionally substituted with 1 to 5 independently selected halo substituents, or with 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents;

Ph^2 is phenyl substituted with:

a) 1 to 5 independently selected halo substituents; or

b) 1 to 3 substituents independently selected from the group consisting of halo, cyano, $-SCF_3$, nitro, hydroxy, (C_1-C_6)alkyl optionally further substituted with 1 to 6 fluoro substituents, and (C_1-C_6)alkoxy optionally further substituted with 1 to 6 fluoro substituents; or

c) 0, 1, or 2 substituents independently selected from the group consisting of halo, cyano, -SCF_3, methyl, -CF_3, methoxy, -OCF_3, nitro, and hydroxy, together with one substituent selected from the group consisting of

i) (C_1-C_{10})alkyl optionally further substituted with 1 to 6 fluoro substituents or mono-substituted with hydroxy, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl(C_0-C_3)alkyloxy, Het^2-(C_0-C_3)alkyloxy, Ph^1-(C_0-C_3)alkyloxy,

ii) (C_1-C_{10})alkoxy-(C_0-C_3)alkyl optionally further substituted with 1 to 6 fluoro substituents, and optionally further substituted with hydroxy,

iii) (C_1-C_6)alkyl-C(O)-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

iv) carboxy,

v) (C_1-C_6)alkoxycarbonyl optionally further substituted with 1 to 6 fluoro substituents,

vi) (C_1-C_6)alkyl-C(O)-(C_0-C_3)-O- optionally further substituted with 1 to 6 fluoro substituents,

vii) (C_1-C_6)alkylthio-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

viii) (C_1-C_6)alkylsulfinyl-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

ix) (C_1-C_6)alkylsulfonyl-(C_0-C_5)alkyl optionally further substituted with 1 to 6 fluoro substituents,

x) (C_1-C_6)alkylsulfonyl-(C_0-C_3)alkyl-O- optionally further substituted with 1 to 6 fluoro substituents,

xi) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-, optionally further substituted on the cycloalkyl with 1 to 4 substituents selected from methyl and fluoro,

xiii) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-C(O)-,

xiv) (C_3-C_7)cycloalkyl(C_0-C_3)alkyl-O-C(O)-,

xv) $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl-S-,

xvi) $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl-S(O)-,

xvii) $(C_3\text{-}C_7)$cycloalkyl$(C_0\text{-}C_3)$alkyl-$S(O)_2$-,

xviii) Ph^1-$(C_0\text{-}C_3)$alkyl, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents,

xix) Ph^1-$(C_0\text{-}C_3)$alkyl-O-, optionally substituted on the alkyl moiety with 1 to 2 fluoro substituents

xx) Ph^1-$(C_0\text{-}C_3)$alkyl-C(O)-,

xxi) Ph^1-$(C_0\text{-}C_3)$alkyl-O-C(O)-,

xxii) Ph^1-$(C_0\text{-}C_3)$alkyl-C(O)-$(C_0\text{-}C_3)$alkyl-O-,

xxiii) Ph^1-$(C_0\text{-}C_3)$alkylthio,

xxiv) Ph^1-$(C_0\text{-}C_3)$alkylsulfinyl,

xxv) Ph^1-$(C_0\text{-}C_3)$alkylsulfonyl,

xxvi) $Ar^2(C_0\text{-}C_3)$alkyl,

xxvii) $Ar^2(C_0\text{-}C_3)$alkyl-O-

xxviii) Ar^2-$(C_0\text{-}C_3)$alkyl-S-,

xxix) $Ar^2(C_0\text{-}C_3)$alkyl-C(O)-,

xxx) $Ar^2(C_0\text{-}C_3)$alkyl-C(S)-,

xxxi) Ar^2-$(C_0\text{-}C_3)$alkylsulfinyl,

xxxii) Ar^2-$(C_0\text{-}C_3)$alkylsulfonyl,

xxxiii) $Het^1(C_0\text{-}C_3)$alkyl-C(O)- optionally substituted on the Het^1 moiety with Ph^1,

xxxiv) $Het^1(C_0\text{-}C_3)$alkyl-C(S)- optionally substituted on the Het^1 moiety with Ph^1,

xxxv) N-linked Het^1-C(O)-$(C_0\text{-}C_3)$alkyl-O-,

xxxvi) Het^2-$(C_0\text{-}C_3)$alkyloxy,

xxxvii) $R^{26}R^{27}N$-,

xxxviii) $R^{28}R^{29}$-N-$(C_1\text{-}C_3)$alkoxy,

xxxix) $R^{28}R^{29}N$-C(O)-,

xl) $R^{28}R^{29}N$-C(O)-$(C_1\text{-}C_3)$alkyl-O-,

xli) $R^{28}R^{29}N$-C(S)-,

xlii) $R^{30}R^{31}N\text{-}S(O)_2\text{-}$,

xliii) $HON{=}C(CH_3)\text{-}$, and

xliv) $HON{=}C(Ph^1)\text{-}$,

or a pharmaceutically acceptable salt thereof, subject to the following provisos:

a) no more than two of R^1, R^2, R^3, R^4, and R^5 may be other than hydrogen;

b) when R^2 is methyl, then R^1, R^3, R^4, and R^5 are each hydrogen;

c) when R^3 is methyl, then R^2 and R^4 are each hydrogen;

d) when R^3 is methyl, R^7 and R^8 are each –OH, and R^1, R^2, R^4, R^5, and R^9 are each hydrogen, then R^6 is other than cyclohexylthio, furanylthio, or phenylthio; and

e) When R^{12} is $Ar^2\text{-}(C_1\text{-}C_3)$alkyl, then R^7 is other than hydrogen or R^9 is other than chloro.

2. A compound according to Claim 1 wherein R^7 is selected from halo, -CN, and CF_3.

3. A compound according to either Claim 1 or Claim 2 wherein R^7 is chloro.

4. A compound according to any one of Claims 1 to 3 wherein R^6 is $-C{\equiv}C\text{-}R^{10}$.

5. A compound according to any one of Claims 1 to 3 wherein R^6 is $-O\text{-}R^{12}$.

6. A compound according to any one of Claims 1 to 3 wherein R^6 is $-S\text{-}R^{14}$.

7. A compound according to Claim 6 wherein R^6 is $-S\text{-}L\text{-}R^{15}$.

8. A compound according to Claim 7 wherein R^{15} is Ph^2 or Ar^2.

9. A compound according to any one of Claims 1 to 3 wherein R^6 is $-NR^{24}R^{25}$.

10. A compound according to Claim 9 wherein R^{24} is Ph^2-(C_1-C_3) *n*-alkyl-.

11. A compound according to Claim 9 wherein R^{24} is Ar^2-(C_1-C_3) *n*-alkyl-.

12. A Compound according to any one of Claims 9 to 11 wherein R^{25} is hydrogen.

13. A compound according to any one of Claims 1 to 12 wherein R^9 is hydrogen, halo or (C_1-C_3)alkoxy.

14. A compound according to any one of Claims 1 to 12 wherein R^9 is hydrogen.

15. A compound according to any one of Claims 1 to 14 wherein R^1, R^2, R^3, R^4, R^5, and R^8, are each hydrogen.

16. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 15 as an active ingredient in association with a pharmaceutically acceptable carrier, diluent or excipient.

17. A compound according to any one of Claims 1 to 15 for use in therapy.

18. A method for the treatment of obesity in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

19. The method of Claim 18, where the mammal is human.

20. A method for the treatment of obsessive compulsive disorder in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

21. The method of Claim 20, where the mammal is human.

22. A method for the treatment of depression in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

23. The method of Claim 22, where the mammal is human.

24. A method for the treatment of anxiety in mammals, comprising administering to a mammal in need of such treatment an effective amount of a compound according to Claim 1.

25. The method of Claim 24, where the mammal is human.

26. A compound according to any one of Claims 1 to 15 for use as a pharmaceutical.

27. A compound according to any one of Claims 1 to 15 for use in the treatment of obesity in mammals.

28. A compound according to any one of Claims 1 to 15 for use in the treatment of obsessive/compulsive disorder in mammals.

29. A compound according to any one of Claims 1 to 15 for use in the treatment of depression in mammals.

30. A compound according to any one of Claims 1 to 15 for use in the treatment of anxiety in mammals.

31. A compound according to any one of Claims 27-30, where the mammal is a human.

32. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, hyperphagia, obsessive/compulsive disorder, depression, anxiety, substance abuse, sleep disorder, hot flashes, and/or hypogonadism.

33. The use of a compound according to any one of Claims 1 to 15 in the manufacture of a medicament for the treatment of a disorder selected from obesity, obsessive/compulsive disorders, anxiety, or depression.

34. A pharmaceutical composition adapted for the treatment of obesity comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

35. A pharmaceutical composition adapted for the treatment of obsessive/compulsive disorders comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

36. A pharmaceutical composition adapted for the treatment of depression comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

37. A pharmaceutical composition adapted for the treatment of anxiety comprising a compound according to any one of Claims 1 to 15 in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents therefore.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US2005/005418

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D223/16 C07D401/12 C07D417/12 C07D413/12 C07D403/12
C07D409/12 C07D405/12 C07D413/14 C07D417/06 C07D403/06
A61K31/55 A61P25/22 A61P25/24 A61P25/30 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93/04686 A (SMITHKLINE BEECHAM CORPORATION) 18 March 1993 (1993-03-18) cited in the application page 11, line 3 - line 18 claim 6	1-37
X	US 4 265 890 A (HOLDEN ET AL) 5 May 1981 (1981-05-05) cited in the application example 19	1-15
Y	WO 93/03015 A (SMITHKLINE BEECHAM CORPORATION) 18 February 1993 (1993-02-18) cited in the application page 11, line 3 - line 18 claim 7	1-37

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 May 2005	02/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Interi al Application No
PCT/US2005/005418

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KILPATRICK, ANDREW T. ET AL: "The .alpha.2-adrenoceptor antagonist SK & F 104078 has high affinity for 5-HT1A and 5-HT2 receptors" EUROPEAN JOURNAL OF PHARMACOLOGY , 166(2), 315-18 CODEN: EJPHAZ; ISSN: 0014-2999, 1989, XP002328505 cited in the application abstract	1-37
A	DATABASE WPI Section Ch, Week 200274 Derwent Publications Ltd., London, GB; Class B02, AN 2002-691852 XP002328506 -& WO 02/074746 A1 (YAMANOUCHI PHARM CO LTD) 26 September 2002 (2002-09-26) cited in the application page 32; examples 75,76	1-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/005418

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18-25
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-25 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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